#### SN 10/563058 Page 167 of 172 STIC STN SEARCH RESULTS

D STAT QUE L33

#### => d his full (FILE 'HOME' ENTERED AT 09:30:05 ON 11 OCT 2007) FILE 'REGISTRY' ENTERED AT 09:30:15 ON 11 OCT 2007 L1STRUCTURE UPLOADED 1 SEA SSS SAM L1 D SCA 560 SEA SSS FUL L1 L3 SAVE TEMP L3 LAO058STR1L/A FILE 'ZCAPLUS' ENTERED AT 09:35:51 ON 11 OCT 2007 L4117 SEA ABB=ON PLU=ON L3 L5 ANALYZE PLU=ON L4 1- RN : 5098 TERMS D D 1-20 FILE 'REGISTRY' ENTERED AT 09:37:09 ON 11 OCT 2007 L6 1 SEA ABB=ON PLU=ON 152044-54-7 1 SEA ABB=ON PLU=ON 152044-53-6 L7 1 SEA ABB=ON PLU=ON 189453-10-9 L8 1 SEA ABB=ON PLU=ON 186692-73-9 L9 1 SEA ABB=ON PLU=ON 187527-25-9 L10 1 SEA ABB=ON PLU=ON 18/32/-25-9 1 SEA ABB=ON PLU=ON 188730-08-7 1 SEA ABB=ON PLU=ON 20949-84-2 1 SEA ABB=ON PLU=ON 106921-60-2 1 SEA ABB=ON PLU=ON 193146-27-9 0 SEA ABB=ON PLU=ON (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 L11 L12 L13 L14 L15 OR L13 OR L14) AND L4 L16 0 SEA ABB=ON PLU=ON (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14) AND L3 1 SEA ABB=ON PLU=ON 186692-84-2 L26 O SEA ABB=ON PLU=ON L3 AND (L6 OR L7 OR L8 OR L9 OR L10 OR L11 L27 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26) L28 191 SEA ABB=ON PLU=ON L3 AND CASREACT/LC FILE 'ZCAPLUS' ENTERED AT 09:43:45 ON 11 OCT 2007 115 SEA ABB=ON PLU=ON L3/P L29 FILE 'CASREACT' ENTERED AT 09:53:42 ON 11 OCT 2007 L30 69 SEA ABB=ON PLU=ON L3 L31 STRUCTURE UPLOADED 0 SEA SUB=L30 SSS SAM L31 ( 0 REACTIONS) L32 23 SEA SUB=L30 SSS FUL L31 ( 468 REACTIONS) L33

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SN 10/563058 Page 168 of 172 STIC STN SEARCH RESULTS
     FILE 'REGISTRY' ENTERED AT 11:21:02 ON 11 OCT 2007
         22933 SEA ABB=ON PLU=ON OC15/ESS
L34
L35
         27330 SEA ABB=ON PLU=ON C16/ESS
           726 SEA ABB=ON PLU=ON NC15/ESS
L36
             O SEA ABB=ON PLU=ON NSC14/ESS
L37
         50989 SEA ABB=ON PLU=ON (L34 OR L35 OR L36 OR L37)
L38
L39
         12165 SEA ABB=ON PLU=ON L38 AND CASREACT/LC
    FILE 'CASREACT' ENTERED AT 11:22:32 ON 11 OCT 2007
          2534 SEA ABB=ON PLU=ON L39/PRO
L40
           59 SEA ABB=ON PLU=ON L30 (L) L40
L41
            65 SEA ABB=ON PLU=ON L3/RRT
L42
L43
            59 SEA ABB=ON PLU=ON L42 (L) L40
            19 SEA ABB=ON PLU=ON L43 AND L33
T.44
    "FILE 'CAPLUS' ENTERED AT 11:34:47 ON 11 OCT 2007
           59 SEA ABB=ON PLU=ON L43
            53 SEA ABB=ON PLU=ON L45 AND PY<2005
L46
            49 SEA ABB=ON PLU=ON L45 AND PY<2004
L47
    FILE 'CASREACT' ENTERED AT 11:35:34 ON 11 OCT 2007
               D L43
            59 SEA ABB=ON PLU=ON L43 AND 1/NS
L49
            50 SEA ABB=ON PLU=ON L43 AND 2/NS
            44 SEA ABB=ON PLU=ON L43 AND 3/NS
L50
            42 SEA ABB=ON PLU=ON L43 AND 4/NS
L51
             9 SEA ABB=ON PLU=ON L48 NOT L49
L52
               D SCA
    FILE 'CAPLUS' ENTERED AT 11:45:06 ON 11 OCT 2007
            45 SEA ABB=ON PLU=ON L45 AND J/DT
L53
            14 SEA ABB=ON PLU=ON L45 AND P/DT
           12 SEA ABB=ON PLU=ON L54 AND PD<20040619
L55
           39 SEA ABB=ON PLU=ON L53 AND ED<20040619
L56
             6 SEA ABB=ON PLU=ON L53 NOT L56
L57
L58
             2 SEA ABB=ON PLU=ON L54 NOT L55
             8 SEA ABB=ON PLU=ON (L57 OR L58)
L59
               SEL AN
    FILE 'CASREACT' ENTERED AT 11:47:33 ON 11 OCT 2007
L60
             8 SEA ABB=ON PLU=ON ("142:134344"/AN OR "143:211773"/AN OR
               "143:422202"/AN OR "144:170808"/AN OR "145:271524"/AN OR
               "145:397261"/AN OR "146:229070"/AN OR "146:251631"/AN OR
               "2004:985335"/AN OR "2005:1154536"/AN OR "2005:1305128"/AN OR
               "2005:614221"/AN OR "2006:1337456"/AN OR "2006:641138"/AN OR
               "2006:66747"/AN OR "2006:805502"/AN)
            51 SEA ABB=ON PLU=ON L48 NOT L60
L61
            42 SEA ABB=ON PLU=ON L49 NOT L60
L62
L63
            36 SEA ABB=ON PLU=ON L50 NOT L60
            35 SEA ABB=ON PLU=ON L51 NOT L60
L64
    FILE 'CAPLUS' ENTERED AT 11:49:27 ON 11 OCT 2007
               E US2006-563058 /APPS
L65
             1 SEA ABB=ON PLU=ON US2006-563058 /AP
               D SCA
               SEL RN
    FILE 'REGISTRY' ENTERED AT 11:50:13 ON 11 OCT 2007
            55 SEA ABB=ON PLU=ON (130486-85-0/BI OR 152044-53-6/BI OR
L66
               152044-54-7/BI OR 185148-95-2/BI OR 220367-73-7/BI OR 220774-16
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-3/BI OR 220774-19-6/BI OR 220774-20-9/BI OR 220774-21-0/BI OR
                220774-22-1/BI OR 220774-23-2/BI OR 220774-57-2/BI OR 220774-58
                -3/BI OR 220774-59-4/BI OR 220774-60-7/BI OR 220774-61-8/BI OR
                220774-62-9/BI OR 220775-18-8/BI OR 220775-76-8/BI OR 289477-70
                -9/BI OR 289477-71-0/BI OR 289477-72-1/BI OR 289477-73-2/BI OR
                289477-74-3/BI OR 303154-55-4/BI OR 303154-56-5/BI OR 303154-57
                -6/BI OR 303154-58-7/BI OR 303154-59-8/BI OR 303154-60-1/BI OR
                305840-13-5/BI OR 823203-01-6/BI OR 823203-02-7/BI OR 823203-03
                -8/BI OR 823203-04-9/BI OR 823203-05-0/BI OR 823203-06-1/BI OR
                823203-07-2/BI OR 823203-08-3/BI OR 823203-09-4/BI OR 823203-10
                -7/BI OR 823203-11-8/BI OR 823203-12-9/BI OR 823203-13-0/BI OR
                823203-14-1/BI OR 823203-15-2/BI OR 823203-16-3/BI OR 823203-17
                -4/BI OR 823203-18-5/BI OR 823203-19-6/BI OR 823203-20-9/BI OR
                823203-23-2/BI OR 823203-24-3/BI OR 823203-25-4/BI OR 823203-27
                -6/BI)
L67
              2 SEA ABB=ON PLU=ON L66 AND L39
                D SCA
     FILE 'CAPLUS' ENTERED AT 11:50:53 ON 11 OCT 2007
L68
              1 SEA ABB=ON PLU=ON L67 AND L65
                D SCA
     FILE 'REGISTRY' ENTERED AT 11:54:40 ON 11 OCT 2007
                E EPOTHILONE C/CN
L69
              1 SEA ABB=ON PLU=ON EPOTHILONE C/CN
                D SCA
L70
              1 SEA ABB=ON PLU=ON EPOTHILONE D/CN
                D SCA
                D RN L67 1-2
     FILE 'CASREACT' ENTERED AT 11:56:56 ON 11 OCT 2007
L71
             21 SEA ABB=ON PLU=ON
                                   152044-54-7/PRO
                           PLU=ON
L72
             14 SEA ABB=ON
                                   152044-53-6/PRO
L73
              7 SEA ABB=ON
                            PLU=ON
                                   L42 (L) L71
L74
              7 SEA ABB=ON
                            PLU=ON
                                   L42 (L) L72
L75
             14 SEA ABB=ON
                            PLU=ON
                                   (L73 OR L74)
L76
             13 SEA ABB=ON
                           PLU=ON L75 NOT L60
     FILE 'CAPLUS' ENTERED AT 11:58:45 ON 11 OCT 2007
L77
             11 SEA ABB=ON PLU=ON L45 AND PY<2000
                SEL AN
     FILE 'CASREACT' ENTERED AT 12:00:01 ON 11 OCT 2007
L78
             11 SEA ABB=ON PLU=ON ("126:251010"/AN OR "127:108793"/AN OR
                "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR
                "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR
                "131:31829"/AN OR "131:351125"/AN OR "132:49832"/AN OR
              .. "1997:206419"/AN OR "1997:430309"/AN OR "1997:665094"/AN OR
                "1997:787450"/AN OR "1998:378435"/AN OR "1999:176999"/AN OR
                "1999:372044"/AN OR "1999:383492"/AN OR "1999:444724"/AN OR
                "1999:606636"/AN OR "1999:819379"/AN)
L79
             11 SEA ABB=ON PLU=ON L78 AND L43
L80
             16 SEA ABB=ON
                           PLU=ON
                                   L79 OR L52
L81
              1 SEA ABB=ON
                           PLU=ON
                                   L80 AND L73
L82
              1 SEA ABB=ON PLU=ON L80 AND L74
L83
             27 SEA ABB=ON
                           PLU=ON L52 OR L79 OR (L81 OR L82) OR L76
             15 SEA ABB=ON
                           PLU=ON L61 NOT L63
L84
                D FHIT 7
L85
             59 SEA ABB=ON
                           PLU=ON L43 (L) 1/NS
             45 SEA ABB=ON PLU=ON L43 (L) 2/NS
L86
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             37 SEA ABB=ON PLU=ON L43 (L) 3/NS
L87
L88
             31 SEA ABB=ON PLU=ON L43 (L) 4/NS
L89
             21 SEA ABB=ON PLU=ON L43 (L) 5/NS
L90
             28 SEA ABB=ON PLU=ON L85 NOT L88
    FILE 'CAPLUS' ENTERED AT 12:09:08 ON 11 OCT 2007
L91
            80 SEA ABB=ON PLU=ON KLAR U?/AU
            116 SEA ABB=ON PLU=ON BUCHMANN B?/AU
L92
           60 SEA ABB=ON PLU=ON SCHWEDE W?/AU
L93
           186 SEA ABB=ON PLU=ON SKUBALLA W?/AU
L94
           32 SEA ABB=ON PLU=ON L91 AND (L92 OR L93 OR L94)
68 SEA ABB=ON PLU=ON L92 AND (L93 OR L94)
L95
L96
            24 SEA ABB=ON PLU=ON L93 AND L94
L97
            25 SEA ABB=ON PLU=ON L95 AND (L96 OR L97)
L98
            24 SEA ABB=ON PLU=ON L96 AND L97
L99
            24 SEA ABB=ON PLU=ON L98 AND L99
L100
             1 SEA ABB=ON PLU=ON L100 AND L43
L101
     FILE 'REGISTRY' ENTERED AT 12:11:27 ON 11 OCT 2007
     FILE 'CAPLUS' ENTERED AT 12:11:29 ON 11 OCT 2007
                D STAT QUE L100
                D IBIB ABS L100 1-24
                D IBIB ABS L100 8-24
             24 SEA ABB=ON PLU=ON L91 AND L92 AND L93 AND L94
L102
                D COST FULL
                D IBIB ABS L102 TOT
                D IBIB L102 10
                D IBIB L102 9
                D ABS L102 8
                D ABS L102 8
                D IBIB ABS L102 9-24
     FILE 'REGISTRY' ENTERED AT 12:16:30 ON 11 OCT 2007
     FILE 'CASREACT' ENTERED AT 12:16:34 ON 11 OCT 2007
                D STAT QUE L33
                D IBIB ABS FHIT L33 1-23
     FILE 'CASREACT' ENTERED AT 12:18:14 ON 11 OCT 2007
                D STAT QUE L90
                D IBIB ABS FHIT L90 1-28
              3 SEA ABB=ON PLU=ON L77 NOT L90
L103
              3 SEA ABB=ON PLU=ON L78 NOT L90
L104
     FILE 'CAPLUS' ENTERED AT 12:40:57 ON 11 OCT 2007
             21 SEA ABB=ON PLU=ON L45 AND PY<2001
L105
                SEL AN
     FILE 'CASREACT' ENTERED AT 12:41:26 ON 11 OCT 2007
             21 SEA ABB=ON PLU=ON ("126:251010"/AN OR "127:108793"/AN OR
L106
                "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR
                "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR
                "131:31829"/AN OR "131:351125"/AN OR "132:251011"/AN OR
                "132:49832"/AN OR "133:266631"/AN OR "133:266634"/AN OR
                "133:321737"/AN OR "133:362657"/AN OR "134:178371"/AN OR
                "134:29228"/AN OR "134:4795"/AN OR "134:56502"/AN OR "135:37156
                6"/AN OR "1997:2,06419"/AN OR "1997:430309"/AN OR "1997:665094"/
                AN OR "1997:787450"/AN OR "1998:378435"/AN OR "1999:176999"/AN
                OR "1999:372044"/AN OR "1999:383492"/AN OR "1999:444724"/AN OR
```

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D IBIB ABS FHIT L109 1-7

#### FILE HOME

#### FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1 DICTIONARY FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

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#### SN 10/563058 Page 172 of 172 STIC STN SEARCH RESULTS

FILE CONTENT: 1840 - 6 Oct 2007 VOL 147 ISS 16

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\* CASREACT now has more than 13.8 million reactions \*

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-> d his full

FILE 'REGISTRY' ENTERED AT 11:21:02 ON 11 OCT 2007
22933 SEA ABB-ON PLU-ON OC15/ESS
27330 SEA ABB-ON PLU-ON C16/ESS
726 SEA ABB-ON PLU-ON NC15/ESS
0 SEA ABB-ON PLU-ON NC15/ESS
50999 SEA ABB-ON PLU-ON 134 ON L35 ON L36 ON L37)
12165 SEA ABB-ON PLU-ON L38 AND CASREACT/LC

L34 L35 L36 L36 L37 L38

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(L6 OR L7 OR L8 OR L9 OR 110 OR L11 OR L12
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          (L6 OR L7 OR L8 OR L9 OR 1.10 OR L11
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   0 REACTIONS)
468 REACTIONS)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        SEA ABB=ON: PLU=ON 70113-32-5
SEA ABB=ON: PLU=ON 186148-95-2
SEA ABB=ON: PLU=ON 186692-84-2
SEA ABB=ON: PLU=ON 13 AND (L6 OR L7 OR L6 OR L12 OR L13 OR L14 OR L15 OR L15 OR L14 OR L22 OR L21 OR L22 OR L23 OR L24 OR L25 OR L25 OR L24 OR L25 O
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     **CASREACT** ENTERED AT 09:53:42 ON 11 OCT 2007 69 SEA ABB=ON PLU=ON L3 STRUCTURE UPLOADED 0 SEA SUB-130 SSS SAM L31 ( 0 REACTION 23 SEA SUB-130 SSS FUL L31 ( 468 REACTION
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               5098 TERMS
                                                                                    FILE 'REGISTRY' ENTERED AT 09:30:15 ON 11 OCT 2007
STRUCTURE UPLOADED
1 SEA SSS SAM L1
D SCA
560 SEA SSS FUL L1
SAVE TEMP L3 LA0058STR1L/A
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             FILE 'REGISTRY' ENTERED AT 09:37:09 ON 11 OCT 2007
                                                                                                                                                                                                                                                                                                                                                                                                            FILE 'ZCAPLUS' ENTERED AT 09:35:51 ON 11 OCT 2007
117 SEA ABB=ON PLU=ON L3
ANALYZE PLU=ON L4 1- RN : 5098 TERN
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          'ZCAPLUS' ENTERED AT 09:43:45 ON 11 OCT 2007
115 SEA ABB-ON: PLU-ON L3/P
(FILE 'HOME' ENTERED AT 09:30:05 ON 11 OCT 2007)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  PLU-ON 187283-46-1
PLU-ON 188899-14-1
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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   OR L13 OR L14) AND L4
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L31
L32
L32
L33
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FILE 'CASREACT' ENTERED AT 11:22:32 ON 11 OCT 2007 2534 SEA ABB=ON PLU=ON L39/PRO 59 SEA ABB=ON PLU=ON L30 (L) L40 65 SEA ABB=ON PLU=ON L3/RT 59 SEA ABB=ON PLU=ON L42 (L) L40 19 SEA ABB=ON PLU=ON L43 AND L33	FILE 'CAPLUS' ENTERED AT 11:34:47 ON 11 OCT 2007 59 SEA ABB=ON PLU=ON L43 53 SEA ABB=ON PLU=ON L45 AND PY<2005 49 SEA ABB=ON PLU=ON L45 AND PY<2004	FILE 'CASREACT' ENTERED AT 11:35:34 ON 11 OCT 200';  D L43  59 SEA ABB=ON PLU-ON L43 AND 1/NS  50 SEA ABB=ON PLU-ON L43 AND 2/NS  44 SEA ABB=ON PLU-ON L43 AND 3/NS  42 SEA ABB=ON PLU-ON L43 AND 4/NS  9 SEA ABB=ON PLU-ON L48 NOT L49  D SCA  D SCA	FILE 'CAPLUS' ENTERED AT 11:45:06 ON 11 OCT 2007 45 SEA ABB-ON PLU-ON 1.45 AND J/DT 14 SEA ABB-ON PLU-ON 1.45 AND P/DT 15 SEA ABB-ON PLU-ON 1.54 AND P/DC20040619 39 SEA ABB-ON PLU-ON 1.53 AND ED<20040619 6 SEA ABB-ON PLU-ON 1.53 NOT 1.56 2 SEA ABB-ON PLU-ON 1.54 NOT 1.55 8 SEA ABB-ON PLU-ON 1.54 NOT 1.55 8 SEA ABB-ON PLU-ON 1.57 OR 1.58) 8 SEL AN	FILE 'CASREACT' ENTERED AT 11:47:33 ON 11 OCT 2007  8 SEA ABB=ON PLUJ=ON ("142:11434",AN OR "143:211773",AN OR "143:12202",AN OR "144:1708",AN OR "145:271524",AN OR "143:397261",AN OR "146:251631",AN OR "165:39761",AN OR "2005:115456",AN OR "2005:115451631",AN OR "2006:14021",AN OR "2005:115456",AN OR "2006:641138",AN OR "2006:66747",AN OR "2006:805502",AN)  51 SEA ABB=ON PLUJ=ON L49 NOT L60  42 SEA ABB=ON PLUJ=ON L50 NOT L60  35 SEA ABB=ON PLUJ=ON L51 NOT L60  35 SEA ABB=ON PLUJ=ON L51 NOT L60	71 2 058	FILE 'REGISTRY' ENTERED AT 11:50:13 ON 11 OCT 2007 55 SEA A3B=ON PLU=ON (130486-85-0/BI OR 152044-53-6/BI OR 220774-16 152044-54-7/BI OR 185148-95-2/BI OR 220367-73-73-7/BI OR 220774-16
141 142 143 1443	1.45 1.46 1.47	148 149 150 151 152	153 154 155 156 157 158 159 159	L60 L61 L63 L63 L63	165	Te6

# SN 10/563058 Page 165 of 172 STIC STN SEARCH RESULTS

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

RCT H 188730-19-0 RX (3) RGT J 4136-95-2 2,4,6-C13C6H2COC1, K 121-44-8 Et3N SOL 109-99-9 THF

STAGE(2) RGT L 1122-58-3 4-DMAP SOL 108-88-3 PhMe

PRO I 186692-84-2 NTE key step REFERENCE COUNT: 100

THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L90 ANSWER 28 OF 28 CASREACT ACCESSION NUMBER: 126:25 TITLE:

SREACT COPYRIGHT 2007 ACS on STN 1 126:251010 CASREACT FULL-text Total synthesis of epothilone A: the macrolactonization approach 3: Nicolaou, K. C.; Sarabia, Francisco; Ninkovic, Sacha;

AUTHOR(S):

SOURCE:

Yang, Zhen Dep. Chem., Skaggs Inst. Chem. Biol., Scripps Res. CORPORATE SOURCE:

Inst., La Jolle, CA, 92037, USA Angewendte Chemie, International Edition in English (1997), 36(5), 525-527 CODER: ACIENY, ISSN: 0570-0833

VCH. Journal English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

Me3CMe2SiO

Epothilone A (I) was prepared via a highly convergent and flexible route with macrolactonization of hydroxy acid II as the key step. æ

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RX(4) OF 4

SN 10/563058 Page 166 of 172 STIC STN SEARCH RESULTS

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

RCT M 188730-19-0 RX (4) STACE(1)
RGT O 4136-95-2 2,4,6-C13C6H2COC1, P 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2) RGT Q 1122-58-3 4-DMAP SOL 108-88-3 PhMe

PRO N 186692-84-2 NTE key step REFERENCE COUNT: 27

THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

#### SN 10/563058 Page 163 of 172 STIC STN SEARCH RESULTS

H YIELD 758

9

RCT G 201136-77-8 RX(2)

RGT I 4136-95-2 2,4,6-C13C6H2COC1, J 121-44-8 Et3N SOL 109-99-9 THF STAGE(1)

STAGE(2) RGT K 1122-58-3 4-DMAP SOL 108-88-3 PhMe

THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT 20 PRO H 201136-78-9.

127:293040 CASREACT Full-text
Total Syntheses of Epothilones A and B
Meng, Dongfang' Bertinato, Peter; Balog, Aaron; Su,
Dei-Shi; Kamenecka, Ted; Sorensen, Erik; Danishefsky, Samuel J. Leboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, Journal of the American Chemical Society (1997), COPYRIGHT 2007 ACS on STN 119(42), 10073-10092 CODEN: JACSAT; ISSN: 0002-7863 American Chemical Society Journal English CASREACT L90 ANSWER 27 OF 28 ACCESSION NUMBER: CORPORATE SOURCE: PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI TITLE: AUTHOR(S): SOURCE:

SN 10/563058 Page 164 of 172 STIC STN SEARCH RESULTS

Four distinct ring-forming strategies were pursued. Of these four, three were reduced to practice. In one approach, the action of a base on a substance possessing an acetate ester and a nonenolizable aldehyde brought about a remarkably effective macroaldolization simultaneously creating the C2-C3 bond and the hydroxyl-bearing stereocenter at C-3. Alternatively, the 16-membered macrolide of the epothilones could be fashioned through a C12-C13 ring-closing oldelin metathesis and through macrolactonization of the appropriate hydroxy development of a novel cyclopropane solvolysis strategy for incorporating the diene-aldehyde cyclocondensation (LACDAC) and asym. allylation methodol. are permitted the establishment of a cis C12-C13 olefin, thus setting the stage acid. The application of a stereospecific B-alkyl Suzuki coupling strategy geminal Me groups of the epothilones, and the use of Lewis acid catalyzed for an eventual site- and diastereoselective epoxidn. reaction. also noteworthy.

H ces I... RX(3) OF 59

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#### SN 10/563058 Page 161 of 172 STIC STN SEARCH RESULTS

RX(1) OF 1 A ===>

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RX(1) RCT A 201136-77-8

STAGE(1) RGT C 121-44-8 Et3N, D 4136-95-2 2,4,6-Cl3C6H2COCl SOL 109-99-9 THF

STAGE (2) RGT E 1122-58-3 4-DMAP SOL 108-88-3, PhMe

PRO B **209260-71-9** REFERENCE COUNT: 40

40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 26 OF 28 CASREACT COPPRIGHT 2007 ACS on STN
ACCESSION NUMBER:
128:101936 CASREACT Full-text
TOTAL synthesis of 26-hydroxyepothilone B and related analogs
AUTHOR(S):
Sarabia, Frantisco, ii, Tanhu
CORPORATE SOURCE:
Department of Chemistry and Biochemistry, University of California, California, 92093, USA
SOURCE:
Chemical Communications (Cambridge) (1997), (24), 2343-2344
CODEN: CHOES; ISSN: 1359-7345
PUBLISHER:
BOCOMENT TYPE:
ROYAL Society of Chemistry
JOURNAL
GRAPHS SOCIETY OF CHEMISTRY
JOURNAL
JOURNAL
GRAPHS SOCIETY OF CHEMISTRY
JOURNAL

SN 10/563058 Page 162 of 172 STIC STN SEARCH RESULTS

AB A series of 26-substituted epothilones B, e.g. I, were constructed by total synthesis involving a selective Wittig olefination, an aldol reaction and a macrolactonization as key steps.

RX(2) OF 2 G ===>

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### SN 10/563058 Page 159 of 172 STIC STN SEARCH RESULTS

methodology for the rapid, highly selective and convergent construction of epothilone  ${\tt B}$ 

Nicolaou, K. C.; Hepworth, David; Finlay, M. Ray V.; Paul King, N.; Merschkun, Barbara; Bigot, Antony Department of Chemistry, The Skagas Inst. Chem. Biol., The Scripps Res. Inst., La Jolla, CA, 92037, USA Chemical Communications (Cambridge) (1999), (6),

CORPORATE SOURCE:

SOURCE:

AUTHOR(S):

CODEN: CHOOFS; ISSN: 1359-7345 Royal Society of Chemistry 519-520

English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

During a synthesis of 16-desmethylepothilone B (1) new methods for the convergent and highly stereoselective synthesis of epothilone B and analogs were developed. Æ

ğ **\===** BL AH RX(18) OF 37

ВK

#### SN 10/563058 Page 160 of 172 STIC STN SEARCH RESULTS

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

RCT BK 226940-48-3, BL 108-88-3 RX(18)

RGT BR 4136-95-2 2,4,6-Cl3C6H2COCl, BC 121-44-8 Et3N SOL 109-99-9 THF STAGE(1)

STAGE (2)

CAT 1122-58-3 4-DMAP SOL 108-88-3 PhMe

THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT BQ **226940-49-4** key step 13 REFERENCE COUNT: PRO

129:189151 CASREACT Full-text
Total synthesis of 26-hydroxy-epothilone B and related analogs via a macrolactonization based strategy
Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha; Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Tetrahedron (1998), 54(25), 7127-7166 CODEN: TETRAB: ISSN: 0040-4020 Elsevier Science Ltd. COPYRIGHT 2007 ACS on STN USA Sarabia, Francisco Jolla, CA, 92037 CASREACT L90 ANSWER 25 OF 28 ACCESSION NUMBER: CORPORATE SOURCE: DOCUMENT TYPE: LANGUAGE: GI AUTHOR(S): PUBLI SHER: SOURCE: rite:

The chemical synthesis of a series of 26-substituted epothilones B was described. Fully protected 26-hydroxydesoxy-epothilone B I (R = SiMe2CMe3, RI = CPH3), prepared via a macrolactonization strategy, served as a common precursor to the designed epothilones described. The synthesized compds. were members of a large epothilone library of a number of antitumor agents. AB

### SN 10/563058 Page 157 of 172 STIC STN SEARCH RESULTS

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

RCT T 241129-39-5 RX (4)

NGT V 84033-23-8 Benzoyl chloride, trichloro-, W 121-44-8 Et3N SOL 109-99-9 THF STAGE(1)

RGT X 1122-58-3 4-DWAP SOL 108-88-3 PhMe, 109-99-9 THF STAGE (2)

PRO U **241129-40-8**REFERENCE COUNT: 12

THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT

COPYRIGHT 2007 ACS on STN CASREACT Full-text 131:31829 CASREACT L90 ANSWER 23 OF 28 ACCESSION NUMBER:

A process for the preparation of ring-opened epothilone intermediates which are useful for the Kim, Soong-Hoon; Borzilleri, Robert M. preparation of epothilone analogs

Bristol-Myers Squibb Company, USA PCT Int. Appl., 20 pp. CODEN: PIXXD2 INVENTOR(S): PATENT ASSIGNEE(S):

Pațent English DOCUMENT TYPE: LANGUAGE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

B 8 8 8 19981130 APPLICATION NO. 9990610 DATE KIND WO 9927890 PATENT NO.

g 5 E S 유**.** UG, ZW, AT, BE, C MC, NL, PT, SE, E SN, TD, TG SZ, SD, £, & ફેં

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19981013 20020402 19990610

CA 1998-2312098 19981130 EP 1998-960564 19981130 GB, GR, II, LL, LU, NL, SE, MC, PT, 19981130 19981130 US 1998-170582 CA 1998-2312098 EP 1998-960564 A1 20000920 CH, DE, DK, ES, FR, B2 AT, BE, IE, FI R: AT, US 6365749 CA 2312098 EP 1035824

AU 1999-16134 JP 2000-522878 ZA 1998-10993 US 1997-67550P WO 1998-US25408 20011011 20000601 PRIORITY APPIN. INFO.: 2003522722 ZA 9810993 AU 739380 JP 2003522

19981201 19971204 19981130

MARPAT 131:31829 OTHER SOURCE(S): GI

SN 10/563058 Page 158 of 172 STIC STN SEARCH RESULTS

A process to produce ring opened epothilones (I) [NRIR2 = N3, (un)substituted amine) and their use in the preparation of epothilone analogs (II) is presented. Thus, epothilone B is cleaved with NaN3, azide reduced to amine amine) and their use in the preparation of epothilone analogs (II) is presented. Thus, epothilone B is cleaved with NaN3, azide reduced to amine and macrolactamized with diphenylphosphoryl azide to give II in 40% yield. æ

**\===** RX(3) OF 6

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

K 26386-88-9 (Pho)2P(O)N3 J 219989-84-1 E 219990-25-7 RCT RGT PRO SOL RX (3)

68-12-2 DME

131:31819 CASREACT Full-text Synthesis of 16-desmethylepothilone B: improved CASREACT COPYRIGHT 2007 ACS on STN 190 ANSWER 24 OF 28 ACCESSION NUMBER: TITLE:

### SN 10/563058 Page 155 of 172 STIC STN SEARCH RESULTS

...D cmm> B RX(2) OF 215

PAGE 1-B

1 3

STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

D 193146-51-9 B 152044-54-7 RX(2) RCT D PRO B NTE 111
REFERENCE COUNT:

THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 82

SREACT COPYRIGHT 2007 ACS on STN
131:286299 CASREACT FULL-text
New Chemical Synthesis of the Promising Cancer
Commother appositic Agent 12,13-Desoxyapochilone B:
Discovery of a Surprising Long-Range Effect on the CASREACT L90 ANSWER 22 OF 28 ACCESSION NUMBER: TITLE:

Harris, Christina R.; Kuduk, Scott D.; Balog, Aaron; Savin, Ken; Glunz, Peter W.; Danishefsky, Samuel J. Diastereoselectivity of an Aldol Condensation Laboratory for Bioorganic Chemistry, The

Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA

CORPORATE SOURCE:

AUTHOR(S):

155

SN 10/563058 Page 156 of 172 STIC STN SEARCH RESULTS

SOURCE:

Journal of the American Chemical Society (1999), 121(30), 7050-7062 . CODEN: JACSAT; ISSN: 0002-7863

American Chemical Society Journal English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

methylpentenal molety B (III), and the thiazoyl-containing vinyl iodide molety C (IV). It was envisioned that a disaterososlective aldol condensation between an achiral C5-C6 (I2)-metalloenolate derived from construct A and an (S)-2-methylalkanal fragment, B, would generate the desired C6-C7 bond. microtubule assemblies. In vivo studies with 12,13-desoxyepothilone B (dEpoB) (1), have established that the desoxy compound is well tolerated and virtually Second, a B-alkyl Suzuki coupling between the vinyl iodide construct C and an alkyl borane would form the C11-C12 bond. Finally, a late-stage reduction of the C3 ketone to the requisite C3 alc. with high asym. induction would permit cutative against a variety of sensitive and resistant xenegraft tumors in animal models. In light of these discoveries, a chemical synthesis of dEpoB would be able to support a serious and substantial discovery research program directed toward the clin. development of this mol. The overall strategy for this endeavor assumed the ability to synthesize dEpoB from three constructs readily accessible achiral building block. The governing concepts the new introduction of the  $\mathfrak{g},\delta ext{-diketo}$  ester fragment A, into the synthesis as a The epothilones are naturally occurring cytotoxic mols. that possess the remarkable ability to arrest cell division through the stabilization of which include an achiral  $\beta,\delta$ -diketo ester construct A (II), an (S)-2synthesis are described æ

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#### SN 10/563058 Page 153 of 172 STIC STN SEARCH RESULTS

The enantioselective total synthesis of epothilone A was achieved via the catalytic coupling of I and II. The key step in the preparation of I was the catalytic cyanosilylation of III. II was prepared via a catalytic organic acetalization followed by an aldol reaction. æ

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

#### RCT C 188730-19-0 RX (5)

RGT AD 4136-95-2 2,4,6-Cl3C6H2COC1, AE 121-44-8 Et3N STAGE (1)

### SN 10/563058 Page 154 of 172 STIC STN SEARCH RESULTS:

SOL 109-99-9 THF

STAGE(2) RGT AF 1122-58-3 4-DMAP SOL 108-88-3 PhMe

THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT AC 186692-84-2 41 PRO AC REFERENCE COUNT:

Schinzer, Dieter; Bauer, Armin, Schieber, Jennifer Chemisches Institut der Otto-von-Guericke-Universitat, Chemistry--A European Journal (1999), 5(9), 2492-2500 CODEN: CEUJED; ISSN: 0947-6539 Wiley-VCH Verlag GmbH COPYRIGHT 2007 ACS on STN Syntheses of (-)-epothilone Magdeburg, D-39106, Germany 131:351125 CASREACT Journal English CASREACT L90 ANSWER 21 OF 28 ACCESSION NUMBER: AUTHOR(S): CORPORATE SOURCE: DOCUMENT TYPE: LANGUAGE: GI PUBLI SHER: SOURCE:

acid. The first synthesis is based on our preceding paper. The critical trisubstituted double bond C12-13 in our second approach was constructed by a highly efficient Pd-mediated coupling reaction. Ring closure was achieved by scale to provide sufficient material for biol. tests. Thiazole fragment II (TBDMS = SIMe2CMe3) was obtained by an improved route starting from (S)-malic Two efficient routes for the total synthesis of (-)-epothilone B (I) are reported. One strategy is based on ring-closing metathesis, and a second synthesis on a macrolactonization. The key fragments are available on large highly efficient Pd-mediated coupling reaction. macrolactonization. æ

### SN 10/563058 Page 151 of 172 STIC STN SEARCH RESULTS

STAGE (2)

STAGE (3)

SOL 141-78-6 ACOEt

PRO

AL 219989-84-1
PHOSPHATE BUFFER USED INSECOND STAGE
80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS
NT: RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT REFERENCE COUNT:

COPYRIGHT 2007 ACS on STN 6631 CASREACT Full-text 133:266631 CASREACT CASREACT L90 ANSWER 19 OF 28 ACCESSION NUMBER:

AUTHOR(S): CORPORATE SOURCE:

Total Synthesis of Epothilone A

Zhu, Bin, Panek, James S.
Department of Chemistry and the Center for Streamlined Synthesis Maccalf Center for Science and Engineering, Boston University, Boston, MA, 02215, USA organic Letters (2000), 2(17), 2575-2578

CODEN: ORLEF7; ISSN: 1523-7060

American Chemical Society Journal English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

SOURCE:

like mechanism of action. A total synthesis of I is reported, which utilizer chiral silane-based bond construction methodol, to introduce the key C-6 and was established by a lipase-mediated kinetic resolution. The fragments were assembled with a Suzuki coupling reaction and an aldol condensation and cyclized with a Yamaguchi-type macrolactonization reaction. The C-15 stereocenter of fragment (III) Epothilones A (I) and B are potent antitumor natural products with a Taxolsynthesis of I is reported, stereocenters of fragment (II). æ

VIII III > RX(4) OF 6

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RCT V 297131-85-2 RX (4)

W YIELD 738

RGT X 4136-95-2 2,4,6-C13C6H2COC1, Y 121-44-8 Et3N SOL 109-99-9 THF STAGE (1)

RGT Z 1122-58-3 4-DMAP SOL 108-88-3 PhMe STAGE(2)

PRO W 297131-86-3

THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT stereoselective 36 REFERENCE COUNT: NTE

COPYRIGHT 2007 ACS on STN

L90 ANSWER 20 OF 28 CASREACT ACCESSION NUMBER: 132:25

132:251011 CASREACT Full-text Enartioselective total synthesis of epothilone A using TITLE:

Graduate School of Pharmaceutical Sciences, The multifunctional asymmetric catalyses Sawada, Daisuke; Shibasaki, Masakatsu AUTHOR(S): CORPORATE SOURCE:

University of Tokyo, Tokyo, 113-0033, Japan Angewandte Chemie, International Edition (2000), 39(1), 209-213 CODEN: ACIEFS; 1SSN: 1433-7851

SOURCE:

Wiley-VCH Verlag GmbH Journal English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

#### SN 10/563058 Page 149 of 172 STIC STN SEARCH RESULTS

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY \* AVAILABLE VIA OFFLINE PRINT \*

RCT T 219990-25-7 RX (8) STAGE(1) SOL 68-12-2 DMF

STAGE(2) RGT D 144-55-8 NaHCO3, Z 26386-88-9 (PhO)2P(0)N3

PRO I 219989-84-1 REFERENCE COUNT: 3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 18 OF 28 ACCESSION NUMBER: TITLE:

133:321737 CASREACT Full-text
A Novel Application of a Pd(0)-Catalyzed Nucleophilic
Substitution Reaction to the Regio- and
Stereoselective Synthesis of Lactam Analogues of the COPYRIGHT 2007 ACS on STN CASREACT

Epothilone Natural Products Sorzilleri, Robert M.; Zheng, Xiaoping; Schmidt,

AUTHOR(S):

Robert J.; Johnson, James A.; Kim, Soong-Hoon; DiMarco, John D.; Fairchild, Craig R.; Gougoutas, Jack ..; Lee, Francis Y. F.; Long, Byron H.; Vite, Gregory

Divisions of Discovery Chemistry Oncology Drug Discovery and Analytical Research and Development, Bristol-Myers Squibb Pharmaceutical Research ournal of the American Chemical Society (2000), nstitute,

CORPORATE SOURCE:

SOURCE:

122(37), 8890-8897

American Chemical Society English Journal

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

SN 10/563058 Page 150 of 172 STIC STN SEARCH RESULTS

initial total synthesis route to prepare the lactam analog of epothilone C was completed and compared to the more direct semisynthesis approach. All of the desired macrolactams in satisfactory overall yields. The entire three-step sequence was streamlined into a "one-pot" process for the epothilone B-lactam, and macrolactamization of the resulting azide acid intermediates provided the semisynthetic approach starting with the unprotected natural products. Highlighted in this strategy is a novel regio- and stereoselective Pd(0)-catalyzed azidation reaction of a macrocyclic lactone. Subsequent reduction lactam analogs were evaluated in vitro and the results are discussed BMS-247550 (I), which is currently undergoing phase I clin. trials.

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RX(10)

RCT AJ 219990-25-7

RGT AM 26386-88-9 (PhO)2P(O)N3, AB 144-55-8 NAHCO3 SOL 68-12-2 DWF STAGE (1)

### SN 10/563058 Page 147 of 172 STIC STN SEARCH RESULTS

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AVAILABLE VIA OFFLINE PRINT \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -

CG 188730-19-0 RCT RX (27)

RGT CS 4136-95-2 2,4,6-C13C6H2COC1, BE 121-44-8 Et3N SOL 109-99-9 THF STAGE(1)

STAGE(2)

RGT BF 1122-58-3 4-DMAP SOL 108-88-3 PhMe

STEREOSELECTIVE CR 186692-84-2 PRO

THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT NTE S' REFERENCE COUNT:

133:362657 CASREACT Full-text A process for the reduction of oxiranyl epothilones to COPYRIGHT 2007 ACS on STN olefinic epothilones CASREACT L90 ANSWER 17 OF 28 ACCESSION NUMBER: TITLE:

Kim, Soong-Hoon; Johnson, James A. Bristol-Myers Squibb Co., USA PCT Int. Appl., 19 pp. CODEN: PIXXD2 INVENTOR(S):
PATENT ASSIGNEE(S):
SOURCE:

English Patent DOCUMENT TYPE: LANGUAGE:

SOUNT: FAMILY ACC. NUM. COPATENT INFORMATION:

9;4,ĕ;º SG, US, ્કું ફ્રે APPLICATION NO. BG, ð 88 E, AZ, ES, 20001130 DATE æ, A, W KIND AE, AL, CZ, DE, IN, IS, MD, MG, WO 2000071521 PATENT NO.

#### STIC STN SEARCH RESULTS SN 10/563058 Page 148 of 172

PT, 명당 83 NL, SE, MC, ZW BE, CH, C SE, BF, E 20000515 0010912 Ľ, JP 2000-619778 IN 2001-M1106 MX 2001-PA11053 US 1999-316796 US 1997-67549P US 1998-82563P US 1998-170581 CA 2000-2375029 EP 2000-930725 UA, UG, UZ, VN, YU, SL, SZ, TZ, UG, ZW, IE, IT, LU, MC, NL, GR, IT, LI, 8 FR, 20011120 20001130 20020213 DK, ES, 1 20030107 20070420 20020722 35, SB, # ¥ € 6 E, S, E, DE, TJ, <del>й</del> PRIORITY APPLN. INFO.: JP 2003500394 IN 2001MN01106 MX 2001PA11053 AT, BE, ж, ж, US 6320045 CA 2375029 EP 1178968

MARPAT 133:362657

OTHER SOURCE(S): GI

alkanoyl, aroyl, silyl, etc.; W = O, NRB; RB = H, OH, alkyl], were prepared via reduction of the corresponding 12,13-epoxyepochilones using a metal or metal-assisted reagent was selected from the group consisting of seective metallocenes, [N2C(COZMe)2, cat Rh2(OAc)4, (N2C(COZMe)2, cat Rh2(OAc)4), (RG(COZMe)2, cat(n-C7H15COZ)2Rh]2], [Zn-Cu, EtOH], [Mg(Hg), MgBr], Cr, dichloride in THF to give epothilone C, a 12(13)-(2)-olefin, in 80% yield -BuLi], [TiCl3, LiAlH4], [TiCl4, Zn], [WCl6, LiAlH4], [NbCl5, [VCl3,Zn], or [WCl6, n-BuLi]. Thus, epothilone A, a 12,13reduced using magnesium turnings and cycloalkyl; R7 = H, alkyl, FeC13, n-BuLi] NeAl H4], 2

RX(8) OF 18

#### SN 10/563058 Page 145 of 172 STIC STN SEARCH RESULTS

11.

these lactams. Using our fully synthetically derived lactams, in vitro and in vivo studies were conducted in comparison with advanced clin. candidates, 12,13-desoxyepothilone B and 12,13-desoxyepothilone F, also derived by total efficient and was amenable to the production of significant quantities of

ĸ þ RX(2) OF 2

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT J 350042-12-5 RX (2)

M 7087-68-5 EtN(Pr-1)2, N 148893-10-1 1H-1,2,3-Triazolo[4,5hexafluorophosphate(1-), 3-oxide, 0 39968-33-7 3H-1,2,3-Triazolo[4,5-b]pyridine, 3-hydroxy-68-12-2 DWF, 75-09-2 CH2Cl2 b]pyridinium, 1-[bis(dimethylamino)methylene]-, STAGE (1) SOL

STAGE(2) RGT P 64-19-7 ACOH SOL 7732-18-5 Water, 109-99-9 THF

PRO K 277749-43-6, L 350042-20-5 REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

COPYRIGHT 2007 ACS on STN CASREACT 134:56502 CASREACT L90 ANSWER 16 OF 28 ACCESSION NUMBER:

TITLE:

AUTHOR(S):

CORPORATE SOURCE:

Synthesis of Epothilones A and B Using Multifunctional Asymmetric Catalysis Sawada, Daisuke; Kanai, Motomu; Shibasaki, Masakatsu Graduate School of Pharmaceutical Sciences, The Enantioselective Total

145

SN 10/563058 Page 146 of 172 STIC STN SEARCH RESULTS

University of Tokyo, Bunkyo-ku Tokyo, 113-0033, Japan Journal of the American Chemical Society (2000), 122(43), 10521-10532

CODEN: JACSAT; ISSN: 0002-7863

American Chemical Society Journal English

PUBLISHER: DOCUMENT TYPE:

SOURCE:

LANGUAGE: GI

the conjugate addition of a thiol to an  $\alpha,\beta$ -unsatd. thioester has been achieved. Epothilones A and B were divided into fragment A (I), fragment B (II), and fragment C (III). A catalytic asym. synthesis of fragments A and B aldol reaction of an unmodified ketone with an aldehyde, and a protonation in by Yamaguchi lactonization as key steps led to an enantiocontrolled synthesis of epothilone A. On the other hand, Suzuki cross\_coupling of fragment B with sis such as a cyanosilylation of an aldehyde, an protonation in the conjugate addition of a thiol to an lpha,eta-unsatd. thioester fragment A with fragment C followed the use of a direct catalytic asym. aldol reaction of an unmodified ketone with an aldehyde as a key step, and the other utilizes a catalytic asym. was accomplished using a catalytic asym. cyanosilylation as a key step. enantiocontrolled synthesis of fragment C was achieved in two ways. synthesis of epothilones A and B using fragment C followed by Yamaguchi lactonization accomplished an enantiocontrolled synthesis of epothilone B Suzuki cross-coupling of An enantioselective total as a key step. ₽9

8 RX(27) OF 319

### SN 10/563058 Page 143 of 172 STIC STN SEARCH RESULTS

TITLE:

Methodology based on chiral silanes in the synthesis of polypropionate-derived natural products - total synthesis of epothilone A Zhu, Bini, Panek, James S.

K. W. Johnson Pharmaceutical Research Institute, Reritan, NJ, 08869, USA AUTHOR(S): CORPORATE SOURCE:

European Journal of Organic Chemistry (2001), (9),

CODEN: EJOCFK; ISSN: 1434-193X Wiley-VCH Verlag GmbH Journal English 1701-1714

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

SOURCE:

H -OSIMe2Bu-t O SiMe2Bu-t

Epothilones A and B are natural products with potent antitumor activity. These Bond construction methodol, based on chiral silanes was utilized to introduce the key C6 and C7 stereocenters of fragment I. A lipase-mediated kinetic Bond Construction mercacenters of fragment I. A lipese-mediated Killette the key C6 and C7 stereocenters of fragment II. The 16-membered resolution established the C15 stereocenter of fragment II. The 16-membered resolution established the C15 stereocenter of fragment II. The 18-membered resolution established the C15 stereocenter of fragment II. compds. have a Taxol-like mechanism of action against tumor cells. A total synthesis of epothilone A is reported, which is based on the synthesis and union of two advanced fragments: C3-C11 fragment I and C12-C21 fragment II. an aldol condensation, and a Yamaguchi-type lactone was constructed using a three-step sequence: an intermol. Suzuki coupling of I and II, macrolactonization reaction. 9

¥ **^==** 3 RX(6) OF 7

AD

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#### SN 10/563058 Page 144 of 172 STIC STN SEARCH RESULTS

9

AE YIELD 73%

AD 297131-85-2 AF 121-44-8 Et3N, AG 4136-95-2 2,4,6-Cl3C6H2COCl AE 297131-86-3 RCT PRGT RX (6)

THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 109-99-9 THF REFERENCE COUNT:

Synthesis and Comparative in Vivo Evaluations of the 15-Aza Epothilones 135:107175 CASREACT Full-text On the Interactivity of Complex Synthesis and Tumor Pharmacology in the Drug Discovery Process: Total COPYRIGHT 2007 ACS on STN CASREACT L90 ANSWER 15 OF 28 ACCESSION NUMBER:

Stachel, Shawn J.; Lee, Chul Bom; Spassova, Maria; Chappell, Mark D.; Bornmann, William G.; Danishefsky, AUTHOR(S):

Facility, The Sloan-Kettering Institute for Cancer, Samuel J.; Chou, Ting-Chao; Guan, Yongbiao Laboratories for Bioorganic Chemistry Preclinical Pharmacology and the Preparative Synthesis Core CORPORATE SOURCE:

Research, New York, NY, 10021, USA Journal of Organic Chemistry (2001), 66(12), 4369-4378 CODEN: JOCEAH; ISSN: 0022-3263 American Chemical Society DOCUMENT TYPE: PUBLI SHER: SOURCE:

English

LANGUAGE:

aza-epothilone B (aza-EpoB; EpoB-lactam). Aza-epothilone B has been advanced to phase I clin. trials by the Bristol-Myers Squibb group. Our synthesis is dEpoB-lactam) and 12,13,15-desoxy-15(R)-aza-epothilone B (15-epi-aza-dEpoB; 15-epi-dEpoB-lactam) have been accomplished via a highly convergent strategy. We have also successfully oxidized 12,13,15-desoxy-15(S)-aza-epothilone B to The total syntheses of 12,13,15-desoxy-15(S)-aza-epothilone B (aza-dEpoB;

### SN 10/563058 Page 141 of 172 STIC STN SEARCH RESULTS

PRO K 219989-84-1.
NTE altornative pre

alternative propn. gave lower yields
THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT

COPYRIGHT 2007 ACS on STN CASREACT

135:180640 CASREACT Full-text
The 12,13-diol cyclization approach for a truly
stereocontrolled total synthesis of epothilone B and
the synthesis of a conformationally restrained analog L90 ANSWER 13 OF 28 ACCESSION NUMBER: TITLE:

Martin, Harry J., Pojarliev, Peter, Kahlig, Hanspeter; Institut fur Organische Chemie der Universitat Wien, CORPORATE SOURCE:

AUTHOR(S):

SOURCE:

Vienna, 1090, Austria Chemistry--A European Journal (2001), 7(10), 2261-2271 CODEN: CEUJED; ISSN: 0947-6539

Wiley-VCH Verlag GmbH Journal English

DOCUMENT TYPE: PUBLI SHER:

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

diastereoselective aldol addition of epoxy-aldehyde IV and the known Southern methylene bridge to give a cyclohexanone derivative. Thus, the Northern hemisphere aldehyde IV was added to the enolate of a cyclohexanone derivative carbon skeleton, containing all the stereogenic centers of I. Functional group manipulation, macrolactonization and removal of two protecting groups then vielded I. The spatial closeness of the C4- $\beta$ -Me and C6-Me group in the been developed. The epoxide moiety in I was generated by regioselective mesylation and base treatment of the 12,13-diol II which was formed by a chelate Gram controlled Grignard addition of (3S)-Br(GH2)3GHMeCH:GH2 and Me hemisphere ketone (S)-MeCH2COCMe2CH(OS1Me2CMe3)CH2CH:CH2 delivered the full Further manipulations and macrolactonization delivered the conformationally A highly convergent and stereoccontrolled synthesis of epothilone B (I) has Both fragments were synthesized from the chiral carbon pool to connect them through precursors (S)-citronellol and (S)-lactic acid, then yielded I. The spatial closeness of th crystal structure of I inspired the authors restrained epothilone derivative V. æ

RX(2) OF 2

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

PAGE 1-B

H YIELD 658

121-44-8 Et3N, J 4136-95-2 2,4,6-C13C6H2COC1, K 1122-58-3 G 263761-19-9 RX (2)

263761-23-5 108-88-3 PhMe PRO

THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT SOL 10 REFERENCE COUNT:

L90 ANSWER 14 OF 28 CASREACT COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 135:137326 CASREACT FULL-text:

# SN 10/563058 Page 139 of 172. STIC STN SEARCH RESULTS

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

(Pho) 2P(0) N3, J 144-55-8 NaHCU3 X 219990-25-7 AC 26386-88-9 (I AB 219989-84-1 RGT PRO RX (8)

68-12-2 DMF REFERENCE COUNT:

THERE ARE 88 CITED REFERENCES. AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

CASREACT L90 ANSWER 12 OF 28 ACCESSION NUMBER: TITLE:

REACT COPYRIGHT 2007 ACS on STN 135:257087 CASREACT Full-text A process for the preparation of epothilone analogs

Li, Wen Sen; Thornton, John E.; Guo, Zhenrong; Swaminathan, Shankar, McConlogue, Gary W. Bristol-Myers Squibb Company, USA PATENT ASSIGNEE(S):

INVENTOR (S):

SOURCE:

PCT Int. Appl., CODEN: PIXXD2

English LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: DOCUMENT TYPE:

多类异岛类 GB, GR, IT, LI, LU, NL, SE, MC, PT, CY, AL, TR # Q 7H, GM, LS, UZ, SE, TG ER, US, 20010312 20010312 20010312 0010312 20020808 AT, UG, ZW, MC, NL, NE, SN, -2404212 MX 2002-PA9165 US 2000-528526 WO 2001-US7749 APPLICATION NO. 2001-US7749 CA 2001-240421; EP 2001-918544 HU 2003-693 JP 2001-568920 NO, 12, SL, SZ, TZ, U IE, IT, LU, N GW, ML, MR, N MW, MX, TM, TR, ş 8,8,8 DK, ES, FR, FI, RO, MK. 20010927 20021218 AU, DK, JP, MK, SL, 8 8 X 20030828 2001002 20050304 20040812 ES, MW, CI, FR, AT, DE, IS, MG, SK, R: AT, BE, CH, DE, DF IE, SI, LT, LIV, FI HU 200300693 AZ 200 JP 2003528990 T 200 IN 2002PN01074 A 200 MX 2002PA09165 A 200 ₹8 S Q is KIND ES, PRIORITY APPLIN. INFO.: ξ, Ŗ WO 2001070716 **克里岛的第四** CA 2404212 EP 1265878 Ŕ PATENT NO. RW:

MARPAT 135:257087

OTHER SOURCE(S): GI

#### SN 10/563058 Page 140 of 172 STIC STN SEARCH RESULTS

sait I (R = NH2, RI = 0-. Bu4N+) in 93% yield. The ring opened epothilone B TBA sait the underwent intramol. macrolactamization using K2CO3, HOBt, and EDCI in THF and DMF to form lactam I (RRI = NH) in 92.7% % yield. The present invention relates to a process for the preparation of epothilone analogs, such as I (RRI = NRI), by initially forming novel ring-posed epothilones and carrying out a macrolactamization reaction thereon. The subject process is amenable to being carried out in a single reaction vessel without isolation of the intermediate compound and provides at least about a three-fold increase in yield over prior processes for preparing the desired epothilone analogs. Thus, ring opening of epothilone B was achieved using NaN3, PMe3 and Bu4N+Cl- in THF in the presence of Pd2(dba)3.CHCl3 to form TE 2

ن : RX(2) OF 4

CM

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT C 361204-09-3 RX (2)

STAGE(1) RGT L 1310-58-3 KOH SOL 109-99-9 THF, 68-12-2 DMF

STAGE(2) RGT M 2592-95-2 1-Benzotriazolol, N 25952-53-8 EDAP

### SN 10/563058 Page 137 of 172 STIC STN SEARCH RESULTS

SOL 109-99-9 THF

RGT AW 1122-58-3 4-DMAP SOL 108-88-3 PhMe STAGE (2)

PRO AU 241129-40-8

Kim, Scong-hoon, Johnson, James A.
Bristol-Myers Squibb Co., USA
U.S., 10 pp., Cont.-in-part of U.S. Ser. No. 170,581.
CODEN: USXXAM
Patent
English
3 REACT COPYRIGHT 2007 ACS on STN 135:371566 CASREACT Full-text Process for reduction of oxiranyl epothilones to olefinic epothilones CASREACT L90 ANSWER 11 OF 28 ACCESSION NUMBER: INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: TITLE:

DOCUMENT TYPE:
LANGUAGE:
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION:

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SN 10/563058 Page 138 of 172 STIC STN SEARCH RESULTS

oxiranyl moiety with a metal or metal-assisted reagent selected from the group consisting of reactive metallocenes, or (WCl6, n-Buil). Thus II was prepared in 29% yield in a multistep reaction from epothilone B via the cycloalkyl or 4-7 membered heterocyclic N-, O-, or S-containing rings;  $I_{\rm c}$  (un)vansbeitured alkyl,  $I_{\rm c}$  (H, (un)vansbeitured o-alkyl, x = GH2 or XY, H; Z = H or OPl where Pl, P2 + H, (un)substituted alkyl, alkanoyl, trialkyl(aryl)silyl) from oxiranyl epothilohes via the reaction of the

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MARPAT 135:371566

OTHER SOURCE(S): GI

#### SN 10/563058 Page 135 of 172 STIC STN SEARCH RESULTS

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APPLICATION NO		WO 20	BB,	Д, ЕС,	Ř,	ĕ	ŢĴ,			II,	Ğ.	WO 2001-US17352		BB,	Ċ E	Ä	ž	ŢĴ,				BF,		AU 20		AU 20	EP 20	GB, GR, IT, LI,	Κ,	JP 20		US 20	us 20	US 20			WO 20	
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																															PRIO							OTHER SOURCE(S): GI

135 naturally occurring polyketides or derivs. thereof. The biol. derived intermediates ("bio-intermediates") generally represent particularly difficult compds. to synthesize using traditional chemical approaches due to one or more modules from one or more polyketide synthase ("PKS") genes that are used starting material in the chemical synthesis of novel mols,, particularly The present invention relates to compds., such as I, made by a subset of 8

#### SN 10/563058 Page 136 of 172 STIC STN SEARCH RESULTS

protocol of Smith and co-workers. By taking advantage of the inherent stereochem, specificity of biol, processes, the syntheses of key intermediates and thus the overall syntheses of compds. like epothilone and discodermolide are greatly simplified. stereocenters. In one aspect of the invention, an intermediate in the synthesis of epothilone is provided that feeds into the synthetic protocol of Danishefsky and co-workers. In another aspect of the invention, intermediates in the synthesis of discodermolide are provided that feed into the synthetic

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RCT AQ 241129-39-5 RX(12)

RGT AV 4136-95-2 2,4,6-C13C6H2COC1, E 121-44-8 Et3N STAGE(1)

#### SN 10/563058 Page 133 of 172 STIC STN SEARCH RESULTS

PATENT NO.	KIND DATE	DATE	APPLICATION NO.	DATE
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DE 10041470	A1	A1 20020228	DE 2000-10041470 20000818	20000818
PRIORITY APPLA. INFO.:			DE 2000-10041470 20000818	20000818
OTHER SOURCE(S):	Æ	MARPAT 136:216592		
19				

$$x^{1} = (CH2)^{n-O} + (CH2)^{n+O} + (CH2)^{n+O}$$

$$x^2 \approx \frac{O - (CH2) n}{(CH2) m - 1 - (CH2) pR26}$$

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According to invention, I can be used alone or for the achievament of additive or symergistic effects in combination with further principles and substance classes applicable in the tumor therapy. Exptl. data from patents .tplbond.C-(GH2)pR26, (GH2)m-C:C-(GH2)pR26, X1, X2; n = 0 - 5; p = 0 - 3; m = 4; R2b = (GH2)m-C:tplbond.C-(GH2)pR26, (GH2)m-C:C- (GH2)pR26, X1, X2; R3a group, halogen; RéRT = C(R33)2, NR32 AY = OC(:0), OCH2. CH2C(:0), NR29C(:0), NR29SO2; DE = CH2CH2, CH2O, OCH2; G = X:CR8-, bicyclic or tricyclic aryl; X = O, (O-alkyl)2, etc.; Z = H, H,OH, H,O-protective group; R8 = H, halogen, CN, C1-20-alkyl, aryl, C7-20-aralkyl; R14 = H, OH, halogen, O-SO2-alkyl, O-SO2-aralkyl; R26 = H, C1-10-alkyl, aryl, C7-20-aralkyl, C1-10-alkyl, aryl, C7-20-aralkyl, C1-10-acyl, OH, O-protecting group; R29 = H, C1-10-alkyl; R32 = H, C1-4-alkyl, C1-4-acyl; R33 = H, halogen), which interact with tubulins by stabilizing the formed microtubulins (no data). I are able specifically to affect cell division and are suitable, for example for the treatment of malignant tumors ovarial -, stomach -, colon -, adeno -, chest -, lungs -, head and neck carcinoma, = H, CI-10-alkyl, aryl, C7-20-aralkyl; R3b = 0-protecting group; R4 = H, C1-10-alkyl, aryl, C7-20-aralkyl, halogen, OH, O-protecting group, CN; R5 = H, C1-10-alkyl, aryl, C7-20-aralkyl, (GH2)s-T; S = 1 - 4; T = OH, O-protecting nalignant melanoma, acute lymphocytic and myelocytic leukemia. In addition I are suitable for the anti-angiogenesis therapy as well as for the treatment o chronic ignitable illnesses (psoriesis, arthritis). For the avoidance of uncontrolled cell rampant growths on as well as the better compatibility of The present invention describes new 6-alkeny1- and 6-alkynylepothilone nedical implants I can be up and/or brought into polymers materials. PCT/EP00/01333 and PCT/IB00/00657 are reproduced here.

#### SN 10/563058 Page 134 of 172 STIC STN SEARCH RESULTS

$$RX(1)$$
 OF 1 A + B ===> C

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

PAGE 2-A a H

RGT RX (1)

C 402476-95-3

7732-18-5 Water, 64-17-5 EtOH PhCH2NEt3 Cl 56-37-1 PRO

136:183657 CASREACT Full-text Process for the blomediated preparation of COPYRIGHT 2007 ACS on STN 136:183657 CASREACT L90 ANSWER 10 OF 28 ACCESSION NUMBER: TITLE:

intermediates for use in the synthesis of polyketides, such as epothilone D and discodermolide Santi, Daniel V.; Ashley, Gary; Myles, David C. Kosan Biosciences, Inc., USA INVENTOR(S): PATENT ASSIGNEE(S):

PCT Int. Appl., 129 pp. CODEN: PIXXD2 English Patent DOCUMENT TYPE: SOURCE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION: LANGUAGE:

### SN 10/563058 Page 131 of 172 STIC STN SEARCH RESULTS

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT C 361204-09-3 RX (2) STAGE(1)

RGT K 584-08-7 K2CO3 SOL 109-99-9 THE, 68-12-2 DMF

STAGE(2)

RGT I 2592-95-2 1-Benzotriazolol, M 25952-53-8 EDAP

PRO J 219989-84-1 NTE alternative prepns. gave lower yields

L90 ANSWER 8 OF 28 CASREACT ACCESSION NUMBER: 136:

136:318824 CASREACT Full-text

136:318824 CASREACT Full-text Synthetic and semisynthetic analogs of epothilones:

chemistry and biological activity

Almann, Karl-Hainz; Blommers, Marcel J. J.; Caravatti, Giorgio; Florsheimer, Andreas; Nicolaou, Kyriacos C.; O'Reilly, Terrence; Schmidt, Alfred;

AUTHOR(S):

Schinzer, Dieter; Wartmann, Markus

CORPORATE SOURCE:

TA Oncology Research, Novartis Pharma AG, Basel,

ACS Symposium Series (2001), 796(Anticancer Agents), CH-4002, Switz.

SOURCE:

CODEN: ACSMCB; ISSN: 0097-6156

American Chemical Society Journal PUBLI SHER:

are naturally occurring microtubule depolymn. inhibitors, which exhibit potent in vitro antiproliferative activity. Epothilone B is a 30-fold more potent inhibitor of human cancer cell growth than paclitaxel in paclitaxel-sensitive cancer cell lines and in paclitaxel-resistant lines exceeds paclitaxel activity by 102 - 103-fold. In addition, epothilone B exhibits potent in vivo antitumor activity even in multidrug-resistant tumor English Epothilones A and B a which exhibit potent DOCUMENT TYPE: LANGUAGE: AB Epothilone

this paper we present the synthesis of these analogs and we discuss the impact of such modifications on tubulin polymerization activity as well as vivo, we have investigated a series of structural modifications involving the equirements for epothilone-mediated cytotoxicity and antitumor activity and to discover analogs with similar potency but perhaps better tolerability in spoxide site (C12/C13) and the heterocyclic side-chain of epothilones. models. In order to gain a better understanding of the structural

ë **8** ∶ RX(32) OF 320

cytotoxicity in vitro.

SN 10/563058 Page 132 of 172 STIC STN SEARCH RESULTS

RCT CP 335160-11-7 RX (32) STAGE (1)

CS 429-41-4 Bu4N.F 109-99-9 THF

RGT CT 4136-95-2 2,4,6-C13C6H2OOC1, AP-121-44-8 Et3N, 1122-58-3 4-DMAP SOL 109-99-9 THF, 108-88-3 PhMe STAGE (2)

RGT R 76-05-1 F3CC02H SOL 75-09-2 CH2C12 STAGE (3)

CR 188260-10-8 PRO CF REFERENCE COUNT:

32

THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD, ALL CITATIONS AVAILABLE IN THE RE FORMAT

136:216592 CASREACT Full-text Procedures for the production of 12,13-COPYRIGHT 2007 ACS on STN 16592 CASREACT Full-text 136:216592 L90 ANSWER 9 OF 28 CASREACT ACCESSION NUMBER: 136:2 TITLE:

cyclopropylepothilone derivatives, as well as for their use in pharmacoutical preparations

Schering Ag, Germany Ger. Offen., 64 pp. CODEN: GWXXBX PATENT ASSIGNEE(S): SOURCE:

Patent German DOCUMENT TYPE:

LANGUAGE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

#### SN 10/563058 Page 129 of 172 STIC STN SEARCH RESULTS

+ STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT.

PAGE 2-A

I YIELD 338

DH 472962-13-3 AN 4136-95-2 2,4,6-C13C6H2COCl, AO 121-44-8 Et3N, AP 1122-58-3 RX (30)

I 472962-14-4', 109-99-9 THF, 108-88-3 PhMe

SOL

stereoselective, Yamaguchi macrocyclization
11 - THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
11 - RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT NTE S REFERENCE COUNT:

A process for the preparation of epothilone analogs and intermediates.
Li, Wen-Sen; Thornton, John E.; Guo, Zhenrong;
Smannathan, Shankar REACT COPYRIGHT 2007 ACS on STN 137:140388 CASREACT Full-text CASREACT L90 ANSWER 7 OF 28 ACCESSION NUMBER: INVENTOR (S): TITLE:

Bristol-Myers Squibb Company, USA PCT Int. Appl., 41 pp. CODEN: PIXXD2 Patent English PATENT ASSIGNEE (S):

DOCUMENT TYPE: SOURCE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION: LANGUAGE:

HK BH, 3 8 3 8 5 1 8 8 8 8 8 .20020122 DATE APPLICATION NO. WO 2002-US1853 20020808 AL, AM, KIND WO 2002060904 WO 2002060904 PATENT NO.

MZ, A X X X BG, KG, MW, MK, MN, SK, SL, E 8 2 2 5 E នុក្ស <del>ខ្</del>មុំ មុ

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4 K 5 BE, SE, TD,

ZW, AT, NL, PT, NE, SN, 20010201 20010905 2001020 ZM, MC, US 2001-775361 US 2001-946721 AU 2002-240014 US 2001-775361 S, B, 톡 17Z, 19 82, SE, S. S. S. 티디 i i i i 9, K. K. K. US 6518421 US 2003004338 AU 2002240014 PRIORITY APPIN. INFO.:

MARPAT 137:140388 OTHER SOURCE(S):

SN 10/563058 Page 130 of 172 STIC STN SEARCH RESULTS ij

present invention relates to a process for the preparation of epothilone is amenable to being carried out in a single reaction vessel three-fold increase in yield over prior processes for preparing the desired epothilone analogs. Thus, ring opening of epothilone B was achieved using MANS, PMSs and Budwoll in THF in the presence of Pd2(deb3)3.CHC13 to form TBA salt I R = NH2, R1 = 0-.Budw+ (III) in 93% yield. III underwent intramol macrolactamization using K2CO3, HOBt, and EDCI in THF and DMF to form II in solation of the intermediate compound and provides at least about ones and carrying out a macrolactamization reaction thereon. B

RX(2) OF 4

20010905

US 2001-946721 US 2000-528526 WO 2002-US1853

#### SN 10/563058 Page 127 of 172 STIC STN SEARCH RESULTS

<u>2</u>

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

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C 361204-09-3 K 584-08-7 K2CO3, L 2592-95-2 1-Benzotriazolol, M 25952-53-8 109-99-9 THF, 68-12-2 DMF J 219989-84-1 RGT SOL SOL RX(2)

deg C SUBSTAGE(1) room temperature -> SUBSTAGE(4) 8 hours, 0 deg C SUBSTAGE(5) 2 hours, 10 deg C 2 hours, SUBSTAGE(2) 5 SUBSTAGE (3)

THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT optimization study

NTE OF REFERENCE COUNT:

L90 ANSWER 6 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 137:310727 CASREACT Full-text
Chemical synthesis and biological evaluation of novel
epothilone B and trans-12,13-cyclopropyl epothilone B

Nicolaou, K. C.; Ritzen, Andreas; Namoto, Kenji; Buey, Ruben M.; Diaz, J. Fernando; Andreu, Jose M.; Markus; Altmann, Karl-Heinz; O'Brate, Wartmann,

Department of Chemistry and Skaggs Institute for Chemistal Biology, Scripps Research Institute, La Jolla, CA, 92037, USA

CORPORATE SOURCE:

SOURCE:

AUTHOR(S):

Tetrahedron (2002), 58(32), 6413-6432 CODEN: TETRAB: ISSN: 0040-4020 Elsevier Science Ltd.

PUBLISHER: DOCUMENT TYPE: LANGUAGE:

SN 10/563058 Page 128 of 172 STIC STN SEARCH RESULTS

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analog of epothilone B I, a series of related trans-12,13-cyclopropyl epothilone B analogs, e.g. II, was accomplished. While the synthesis of the epothilone B analog I proceeded through a Stille coupling of a vinyl iodide substrate containing the epothilone macrocycle with the appropriate side chain stannane, that of the cyclopropyl analogs involved a convergent strategy in which a Nozaki-Hiyama-Kishi coupling was used as a means of introducing the side chains prior to Yamaguchi macrolactonization and final elaboration to the nvolving in vitro tubulin polymerization, affinity for the microtubule Taxol spothilones and shed further light on the structure-activity relationships The synthesized analogs were subjected to biol. evaluation In addition to the total synthesis of the thiomethyl thiazole side chain The results identified the methylthic thiazole side chain as a potency enhancing moiety for the binding site and cell cytotoxicity assays. target mols.

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### SN 10/563058 Page 125 of 172 STIC STN SEARCH RESULTS

RX (3)

252877-37-5 Synthase, epothilone

7732-18-5 Water, 67-68-5 DMSO

enzymic, recombinant epothilone thioesterase 22 hours, 30 deg C, pH 5 biotransformation,

domain used, phosphate-buffered soln., product distribution depends on reaction conditions

29 THEER ARE 29 CITED REFERENCES, AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT REFERENCE COUNT:

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Bristol-Myers Squibb Company, USA U.S., 17 pp., Cont.-in-part of U.S. Ser. No. 528,526. CODEN: USXXAM epothilone analogs 138:153369 CASREACT Full-text Process for the preparation of epothilone anal. Li, Wen Sen; Thornton, John E.; Guo, Zhenrong; COPYRIGHT 2007 ACS on STN Swaminathan, Shankar Patent English CASREACT LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: L90 ANSWER 5 OF 28 ACCESSION NUMBER: PATENT ASSIGNEE(S): DOCUMENT TYPE: INVENTOR (S): SOURCE:

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PATENT NO.	-	5184	2003004338	0020	2002060904							RW:		
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#### SN 10/563058 Page 126 of 172 STIC STN SEARCH RESULTS

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AU 2002240014	A1	20020812	æ	AU 2002-240014	20020122
US 39356	E1	20061017	SD	2005-56606	20050211
PRIORITY APPLN. INFO.:		•	ns	2000-528526	20000320
			SD	2001-775361	20010201
		•	S	2001-946721	20010905
			ş	2002-US1853	20020122
OTHER SOURCE(S):	MAR	MARPAT 138:153369			
GI					

compound and provides at least about a three-fold increase in yield over prior processes for preparing the desired epothilone analogs. Thus, epothilone B I (X = 0) was treated with Navi3 and Bu4M+Cl- in THF followed by addition of water PMe3 in THF and equilibrated to 25° then addition of Pd2(dba)3.GHCl3. The resulting solution was stirred under an argon atmospheric for 19 h. to form ring opened salt II in 96% yield. Salt II was then dissolved in THF and DMF, cooled to -5°, treated with KZOO3 and stirred for 5 min before adding HOBE and EDCI then stirring for 2 h at -5° to form lactam I (X =NH) in 56% amenable to being carried out in a single reaction vessel without isolation of the intermediate the subject process is macrolactamization reaction thereon. yield from epothilone B.

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. RX(2) OF 4

SN 10/563058 Page 123 of 172 STIC STN SEARCH RESULTS RX(38) OF 219

(B)

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA CFFLINE PRINT \*

PAGE 2-A

FIELD 338

RCT DB 611168-66-2 RX (38)

DJ 4136-95-2 2,4,6-Cl3C6H2COCl, BD 121-44-8 Et3N 109-99-9 THF STAGE(1)
RGT D
SOL 1

1 hour, 0 deg C

CF 1122-58-3 4-DMAP 108-88-3 PhMe 3 hours, 75 deg C STAGE(2)

SOL SOL SOL

E 611168-68-4

Yamaguchi raaction, addnl. stereoloomeric reactant present F: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT PRO E 6
NTE Yam
REFERENCE COUNT:

130 ANSWER 4 OF 28 CASREACY COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 138:316732 CASREACT FUll-text
Epothilone C Macrolactorization and Hydrolysis Are
Catalyzed by the Isolated Thiosterase Domain of
Epothilone Polyketide Synthase

SN 10/563058 Page 124 of 172 STIC STN SEARCH RESULTS

CORPORATE SOURCE: AUTHOR(S):

Boddy, Christopher N.; Schneider, Tanya L.; Hotta, Kinya; Walsh, Christopher T.; Khosla, Chaitan Departments of Chemical Engineering, Chemistry and Bochemistry, Stanford University, Stanford, CA, 94305-5025, USA

Journal of the American Chemical Society (2003),

125(12), 3428-3429 CODEN: JACSAT, ISSN: 0002-7863

American Chemical Society Journal

English PUBLISHER: DOCUMENT IYPE:

cyclorelease of epothilone from the EpoF protein. It has been unclear whother isolated PKS TE domains could exhibit macrolactonization activity. Here we demonstrate that the excised apothilone TE domain can catalyze the efficient cyclization of the N-acetylcysteamine thioester of seco-apothilone C to generate apothilone C (kcat/KM =  $0.41\pm0.03\,\mathrm{min}-1\,\mathrm{mV}-1)$ ). The TE domain also catalyses the hydrolysis of both the N-acetylcysteamine thioester of seco-Epothilone C is produced by the combined action of one nonribosomal peptide synthetase (NRPS) and nine polyketide synthase (PKS) modules in a multienzyme system. The final step in the biosynthesis is the thioesterase (TE)-catalyze epothilone C (kcat = 0.087 ± 0.005 min-1, KM = 291 ± 53 µM) and that of the epothilone C (keat = 0.67  $\pm$  0.01 min-1, KM = 117  $\pm$  5  $\mu M$ ) to form seco-epothilone C. LANGUAGE: AB Epotl

...H ----> A... RX(3) OF 8

PAGE 1-B

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### SN 10/563058 Page 121 of 172 STIC STN SEARCH RESULTS

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room temperature -> -5 deg C
                                       60-29-7 Et20, 75-09-2 CH2Cl2
CON 1 hour, room temperature
                                         SOL 60-29-7 Et20, 137
                                                                                                           room temperature
                                                                                            7732-18-5 Water
                                                                                                                                                   109-99-9 THF
                                                                                 STAGE (6)
                            STAGE (5)
                                                                                                                                      STAGE (7)
                                                                                                                                                                                            STAGE (8)
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8 80
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CB 4136-95-2 2,4,6-C13C6H2COC1 SUBSTACE(1) -5 deg C SUBSTACE(2) -5 deg C -> 0 deg C SUBSTACE(2) -5 deg C -> 0 deg C RGT CA 121-44-8 Et3N CON -5 deg C STAGE (9) S G

4 hours, room temperature CC 1122-58-3: 4-DMAP 108-88-3 PhMe STAGE (10) SOL SOL SOL

8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT PRO BW 867376-54-3, BX 867376-57-6 sixth stage quench NTE SI REFERENCE COUNT:

CASREACT COPYRIGHT 2007 ACS on STN 143:211773 CASREACT Full-text Method for synthesis of Epothilon B lactam derivative Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. CODEN: CNXXEV Yan, Jialin Chinese Patent diven LANGUAGE: FAMILY ACC. NUM. COUNT: PAFENT INFORMATION: L90 ANSWER 2 OF 28 ACCESSION NUMBER: PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE: INVENTOR (S): TITLE:

Epothilon B lactam derivative was synthesized from Epothilone B via regional and stereo selective nitridization of the Epsilon B macrolide catalyzed by palladium tri-Ph phosphine. Epothilone B was first ring opened via nitridization reaction to obtain nitronic acid, then processed with tri-Ph phosphine to produce imino phosphorane, later hydrolyzed with ammonium phydroxide to form amino acid, and finally the amino acid was cyclized with DPPA and solid sodium bicarbonate to obtain the target product Epothilone B GN 2003-10112901 20031225 GN 2003-10112901 20031225 20041215 K PRIORITY APPLN. INFO.: AB Epothilon B lactar lactam derivative QN 1554659

APPLICATION NO.

KIND DATE

PATENT NO.

121

SN 10/563058 Page 122 of 172 STIC STN SEARCH RESULTS

**⟨===** 9··· 9 RX(3) OF

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT .

K 144-55-8 NaHCO3, L 26386-88-9 (PhO)2P(O)N3 J 219989-84-1 G 219990-25-7 RGT PRO SOL SOL RX (3)

68-12-2 DMF 24 hours, 4 deg C

139:301287 CASREACT <u>Full-text</u> Design, synthesis, and biological properties of highly potent epothilone B analogues COPYRIGHT 2007 ACS on STN L90 ANSWER 3 OF 28 CASREACT ACCESSION NUMBER: TITLE:

Nicolaou, K. C.; Sasmal, Pradip K.; Rassias, Gerasimos; Reddy, Mali Venkat; Altmann, Karl-Heinz; Wartmann, Markus; O'Brate, Aurora; Giannakakou, AUTHOR(S):

Department of Chemistry, The Skaggs Institute for Chemical Biology The Scripps Research Institute, I Jolla, CA, 92037, USA Paraskevi CORPORATE SOURCE:

Ľa

Angewandte Chemie, International Edition (2003), 42(30), 3515-3520 CODEN: ACIEF5; ISSN: 1433-7851 SOURCE:

Wiley-VCH Verlag GmbH & Co. KGaA English DOCUMENT TYPE: LANGUAGE: AB Epothilone PUBLI SHER:

Epothilones have potent cytotoxicity against tumor cells. We directed our attention toward the synthesis and evaluation of a small designed library of epothilone B analogs. From the library, we found that 12,13-cis-cyclopropane methylsulfanyl epothilone B is extremely potent.

### SN 10/563058 Page 119 of 172 STIC STN SEARCH RESULTS

(TBDMS = SiMe2CWe3) was prepared from camphosultam V via protection with novel reagent, 4-[(trimethylsilyl)methyl]benzyl trichloroacetimidate, basic hydrolysi with LiOH in aqueous THF, stereoselective aldol reaction with undecadenal VI in THF containing LDA, silylation with CF3SQSZIMe2CMe3 in CH2Cl2 containing 2,6-lutidine and regioselective desilylation with MGBF2 in Et2O,MeWO2 containing BUSH, and macrolactonization with 2,4,6-Cl3CGH2COCl in THF containing Et3N followed by DWAP in PhMe.

...BQ + BR ===> BW RX(28) OF 58

PAGE 1-B

SN 10/563058 Page 120 of 172 STIC STN SEARCH RESULTS

(38)

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

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PAGE 2-A

BW YIELD 178

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \* PAGE 2-A

Me ≯e

BX YIELD 33%

RX(28)

STAGE(2) SOL 75-52-5 MeNO2 CON room temperature STAGE (3)

BZ 109-79-5 BuSH room temperature 8 8 8

STAGE(4). RCT BQ 867376-53-2, BR 867376-58-7 SOL 60-29-7 Et20

### SN 10/563058 Page 117 of 172 STIC STN SEARCH RESULTS

STAGE(2) RGT Z 1122-58-3 4-DMAP SOL 108-88-3 PhMe

AH 240816-03-9 PRO

key step

THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 9 REFERENCE COUNT:

127:108793 CASREACT Full-teat
127:108793 CASREACT Full-teat
Stereoselective syntheses and evaluation of compounds in the 8-desmethylepothilone A series: some surprising observations regarding their chemical and biological L109 ANSWER 7 OF 7 CASREACT ACCESSION NUMBER: 127: ITILE:

Balog, Aaron; Betinato, Peter; Su, Dai-Shi; Meng,

AUTHOR(S):

Dongfang; Sorensen, Erik; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.

Lab. Bioorganic Chem., Sloan-Kettering Inst. Cancer Res., New York, NY, 10021, USA Tetrahedron Letters (1997), 38(26),:4529-4532 CODEN: TELEAY, ISSN: 0040-4039 CORPORATE SOURCE:

SOURCE:

The title compds. have been synthesized in a convergent way by recourse to Elsevier Journal DOCUMENT TYPE: PUBLI SHER: LANGUAGE:

Weiler type dianion construction.

===> i T. RX(3) OF 15

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

SN 10/563058 Page 118 of 172 STIC STN SEARCH RESULTS

N 1122-58-3 4-DMAP RGT I 192370-80-2 RGT M 538-75-0 DCC, PRO L 192370-81-3 67-66-3 CHC13 RX (3)

REFERENCE COUNT:

THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Novel protecting reagents, protecting groups and methods of forming and using the same Avery, Mitchell A.; Chittiboyina, Amar Gopal; Chada, Raji Reddy; Kache, Rajashaker; Jung, Jae Chul The University of Mississippi, USA PCT Int. Appl., 82 pp. CODEN: PIXKDZ APPLICATION NO. L90 ANSWER 1 OF 28 CASREACT COPYRIGHT 2007 ACS on STN CASREACT 143:422202 English Patent KIND FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT ASSIGNEE(S): ACCESSION NUMBER: PATENT NO. DOCUMENT TYPE: INVENTOR(S): LANGUAGE SOURCE: TITLE:

Š NA, SL, ZW, ZW, GW, GW, US 2004-555896P 20040323 S # 8 # 8 BW, MARPAT 143:422202 20051027 ### 3 6 8 F 5 Ę KG, PRIORITY APPLN, INFO. OTHER SOURCE(S): SE, 88 ES WO 2005100329 SY, SK RW:

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

TIX-Y reagents are 2, 3, and 4-trialkylsilylxylyl, triarylsilylxylyl or a combination of alkyl-aryl silylxylyl reagents [TIX reagents, I (R, R'', R''' alkyl, aryl), II (R, R'', R''' = alkyl, aryl) and III (R, R'', R''' = alkyl, Thus, epothilone derivative IV New protecting reagents TIX-Y (Y = OCNHCC13, Cl, Br, I, NCO, OCOC1, OCH2C1, OTS, OMS, ONS, OTf) are provided that allow for the selective placement of a new protecting group onto a reactive site of a multifunctional compound The hydroxyl groups, amine groups, or thiol groups; methods of removing the TIX protecting groups; and intermediate compds. formed during any one of these aryl)), which carry a TIX protecting group for protecting alcs. as ethers, urethanes, carbonates, acetals; amines as carbamates or uress; and thiols a ethers or esters. The invention also provides methods of forming the 2, 3, and 4-TIX reagents; introducing the TIX protecting groups to mols. bearing The invention further provides methods useful in producing epothilones and analogs and derivs. thereof. B

#### SN 10/563058 Page 115 of 172 STIC STN SEARCH RESULTS

RGT X 4136-95-2 2,4,6-C13C6H2COC1, O 121-44-8 Et3N SOL 109-99-9 THF STAGE(1)

RGT Y 1122-58-3 4-DMAP SOL 108-88-3 PhMe STAGE(2)

W 226940-49-4 key step PRO

131:199535 CASREACT Full-text
Total synthesis of epothilone E and related side-chain modified analogues via a Stille coupling based Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D. Depriment of Chemistry and The Skagg Institute for Chemical Biology, The Scripps Research Institute, La COPYRIGHT 2007 ACS on STN strategy L109 ANSWER 6 OF 7 CASREACT ACCESSION NUMBER: 131: TOTA CORPORATE SOURCE: AUTHOR(S):

Jolla, CA, 92037, USA Bioorganic & Medicinal Chemistry (1999), 7(5), 665-697 CODEN: BMECEP, ISSN: 0968-0896

Elsevier Science Ltd. Journal English PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

SOURCE:

2

and its trans-isomer III (R3 = I) A Stille coupling strategy has been utilized to complete a total synthesis of epothilone E from vinyl iodide I (Rl = I; R2 = H) and thiszolestannane II. The central core fragment I (Rl = I; R2 = H) and its trans-isomer III (R3 = I) were prepared from triene IV (TBS = SiMe2CMe3) using ring-closing metathesis (RCM), and were subsequently coupled to a variety of alternative stannanes to æ

115

#### SN 10/563058 Page 116 of 172 STIC STN SEARCH RESULTS

yl, 2-(methylthio)thiazol-4-yl, 2-piperidinothiazol-4-yl, 2-methoxythiazol-4-yl, 2-ethoxythiazol-4-yl, thiazol-4-yl, thiazol-2-yl, thiazol-5-yl, 2-(hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-ethylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-thienyl, Ph,3-pyridyl, GH:C(ethyle) (2-fired) acetoxypentyl)thiazol-4-yl, 2-(methylthio)thiazol-4-yl, 2-piperidinothiazol-4-yl, 2-piperidinoth thiazol-5-yl, 2-(hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(fluoromethyl)thiazol-4-yl, 2-vinylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-furyl, 2-thianyl, Ph,3-pyridyl, GH:C(OEI/Me-C2). The Stille coupling approach was then used to prepare epothilone B analogs from the key macrolactone intermediate I (RI = I, R2 = CH2OH) which was itself synthesized by a provide a library of epothilone analogs I [R1 = 2-(5-acetoxypenty1)thiazol-4yl, 2-methoxythiazol-4-yl, 2-ethoxythiazol-4-yl, thiazol-4-yl, thiazol-2-yl, macrolactonization based strategy.

...BT acm > AH... RX(19) OF 264

AH YIELD 848

RCT BT 240816-02-8 RX (19)

CB 4136-95-2 2,4,6-C13C6H2COC1, BW 121-44-8 Et3N 109-99-9 THF STAGE (1)

### SN 10/563058 Page 113 of 172 STIC STN SEARCH RESULTS

PAGE 1-B

<u>2</u>

+ STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT AY 298702-20-2 RX(12) STAGE(1) RGT N 121-44-8 Et3N, BB 50-43-1 Benzoic acid, 2,4,6-trichloro-SOL 109-99-9'THF

RGT BC 1122-58-3 4-DMAP SOL 108-88-3 PhMe STAGE(2)

STEREOSELECTIVE PRO BA 298702-21-3 NTE STEREOSELECTIVE REFERENCE COUNT: 51

THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Preparation of 16-desmethylepothilones for the ACT COPYRIGHT 2007 ACS on STN 132:49832 CASREACT Full-text CASREACT L109 ANSWER 5 OF 7 ACCESSION NUMBER: TITLE:

treatment of proliferative diseases. Nicolaou, Kyriacos Costa; Hepworth, David; Finlay, Maurice Raymond Verschoyle; King, Nigel Paul Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.; Scripps Research PATENT ASSIGNEE (S):

INVENTOR(S):

Institute

PCT Int. Appl., 31 pp. CODEN: PIXXD2 Patent DOCUMENT TYPE: SOURCE:

English LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	1			
WO 9967253	A2	A2 19991229	WO 1999-EP4299	19990621
WO 9967253	A3	20000420		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN,	AM. AT.	AU. AZ, BA, BB	, BG, BR, BY, CA	£, £,

STIC STN SEARCH RESULTS SN 10/563058 Page 114 of 172

1S, 8,8 IN, MG, 1 DE, CF, 유, 요, 타, 원, 19990621 19980622 19980622 19990306 BE, NA, YU, ZA, ZW SZ, UG, ZW, AT, BI LU, MC, NL, PT, SI NE, SN, TD, TG US 1999-102602 AU 1999-47752 US 1999-1221559 US 1999-124653P US 1999-124653P US 1996-32864P US 1997-856533 US 1997-923869 WO 1999-EP4299 GM, HR, H LS, LT, I SD, SE, S ¥233€ 935 20020430 20000110 GB, KZ, PL, KX, XX, કું કુ κε, FR, ES, Ω, Ω, EE, I 

MARPAT 132:49832 OTHER SOURCE(S): GI

19990621

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

synthesis of I, as well as for the synthesis of epothilone B (II) and their intermediates. Thus, 16-desmethyldesoxyepothilone analog III was prepared via Yamaguchi macrolactonization of hydroxy acid IV. The compds. I can be used and methods of The invention relates to compds. I  $\{X = bond, 0; Q = OH, A = bond, O;  e.g. in the treatment of proliferative diseases B

... W. ... **.**.. RX(4) OF 46

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT J 252986-91-7 RX (4)

113

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### SN 10/563058 Page 111 of 172 STIC STN SEARCH RESULTS

NTE STEREOSELECTIVE REFERENCE COUNT: 22

THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 3 OF 7 CASREACT ACCESSION NUMBER: 134

EACT COPYRIGHT 2007 ACS on STN 134:4795 CASREACT FULL-text Total Syntheses of Epothilones B and D Mulzer, Johann, Mantoulidis, Andreas; Oehler, Lisabeth Institut fuer Organische Chemie, Universitaet Wien,

AUTHOR(S):

SOURCE:

Vienna, A-1090, Austria Journal of Organic Chamistry (2000), 65(22), 7456-7467 ODEN: JOCEAH; ISSN: 0022-3263 American Chemical Society CORPORATE SOURCE:

and D are described, starting from optically pure (S)-malic acid and Me (R)-3-hydroxy-2-methylpropionate. The synthesis is highly convegent by coupling the three fragments C1-C6 (fragment D),  $\mathcal{C}J$ -C10 (fragment C), and C11-C21 (fragment B). Key steps are two stereoselective Wittig type olefinations to the microtubule stabilizing antitumor drugs epothilone B aldol addition to synthesize fragment D, and a sulfone anion allyl iodide alkylation to connect fragments B and C. Finally fragment D was attached to generate the 12,13- and 16,17-double bonds, an enantioselective Mukaiyama the B + C fragment via aldol addition English Total syntheses of DOCUMENT TYPE: LANGUAGE: AB Total synt PUBLI SHER:

**\DEB** TO:: RX(34) OF 711

Ωľ

33

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT DL 193146-26-8 RX (34)

DN 1122-58-3 4-DMAP, DO 25952-53-8 EDAP, DP 71561-71-2 STAGE (1) RGT

111

SN 10/563058 Page 112 of 172 STIC STN SEARCH RESULTS

4-Me2NC5H4N.HC1 SOL 67-66-3 CHC13

RGT AK 12125-02-9 NH4C1 SOL 7732-18-5 Water STAGE(2)

H 189453-35-8

PRO H REFERENCE COUNT:

THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

CASREACT

JACT COPYRIGHT 2007 ACS on STN 133;266634 CASREACT Full-text L109 ANSWER 4 OF 7 ACCESSION NUMBER:

Journal of Organic Chemiatry (2000), 65(20), 6325-6533 CODEN: JOCEAH; ISSN: 0022-3263 American Chemical Society 133;266634 CASREACT Full-text
Total Synthesis and Antitumor Activity of
12,13-Desoxyeopthilone F: An Unexpected Solvolysis
problem at Cl5, Mediated by Remote Substitution at C21
Lee, Chul Bom; Chou, Ting-Chao; Zhang, Xiu-Guo; Wang,
Zhi-Guang; Kuduk, Soott D.; Chappoll, Mark D.;
Stachs, Shawn J.; Danishefsky, Samuel J.
Laboratory for Bloorganic Chemistry, The Sloan-Kettering Institute for Cancer Research, New York, NY, 1002 CORPORATE SOURCE: PUBLISHER: DOCUMENT IYPE: AUTHOR(S): SOURCE: TITLE:

A пем epothilone analog, 12,13-desoxyapothilone F (dEpoF, 21-hydroxy-12,13-desoxyapothilone B, 21-hydroxyapothilone D), маз synthesized and evaluated for antitumor potential. A convergent strategy employed for the semi-practical The results from an in vitro assay reveal that this new analog is highly active against various tumor cell lines with a potency comparable to that of dEpoB. In particular, the growth of resistant tumor cells is inhibited by dEpoF at concns. where hydroxyl group at C21, exhibits advantages over other epothilones in terms of synthesis of 12,13-desoxyepothilone B (dEpoB) has been utilized to yield an in vivo activity is also promising. The new analog, containing an addnl. and can serve as a readily functionalizable handle to produce other useful compds. for pertinent biol. studies amount of dEpoF sufficient for relevant biol. studies. is basically ineffective. English paclitaxel (Taxol) water solubility, LANGUAGE: AB A nev

---- BA ... **A**Y RX(12) OF 128

### SN 10/563058 Page 109 of 172 STIC STN SEARCH RESULTS

STAGE(2) SOL 108-88-3 PhMe

STAGE(3) RGT AV 1122-58-3 4-DMAP SOL 108-88-3 PhMe

PRO W 279226-97-0 NTE stereoselective REFERENCE COUNT: 25

THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 2 OF 7 CASREACT COPPRIGHT 2007 ACS on STN
ACCESSION NUMBER: 134:29228 CASREACT Full-text
TITLE: A novel highly stereoselective total synthesis of epothlone B and [158 (12R,13R) acetonide Multer, J.; Kerig, G.; Pojatliev, P. Institut fur Organische Chemie der Universitat Wien,

AUTHOR(S): CORPORATE SOURCE:

Tetrahedron Letters (2000), 41(40), 7635-7638 CODEN: TELEAY; ISSN: 0040-4039 Science Ltd.

Journal English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

SOURCE:

Stereoselective syntheses of epothilone B and its novel derivative I are described. Key steps are the formation of intermediate II via Sharpless ADreaction and Davis-Evans-hydroxylation. æ

ö .: A RX(30) OF 447

SN 10/563058 Page 110 of 172 STIC STN SEARCH RESULTS

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VIELD 508

#### RCT CI 312492-96-9 RX (30)

STAGE (1)

RGT CN 429-41-4 Bu4N.F SOL 109-99-9 THF

RGT CO 4136-95-2 2,4,6-C13C6H2COC1, AF 121-44-8 Et3N SOL 108-88-3 PhMe STAGE (2)

RGT CP 1122-58-3 4-DMAP SOL 108-88-3 PhMe STAGE(3)

PRO CM 312492-98-1

#### STIC STN SEARCH RESULTS SN 10/563058 Page 107 of 172

28 SEA FILE=CASREACT ABB=ON PLU=ON L85 NOT L88
21 SEA FILE=CASREACT ABB=ON PLU=ON ("126:25:010"/AN OR "127:1087
93"/AN OR "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN
OR "131:199558"/AN OR "131:286299"/AN OR "131:31819"/AN OR "131:31829"/AN OR "131:31829"/AN OR "131:35125"/AN OR "133:266631"/AN OR "133:266634"/AN OR "133:2666 "133:321737"/AN OR "133:562657"/AN OR "134:178371"/AN OR "135:37156" AN OR "134:17837"/AN OR "135:37156" AN OR "134:575602"/AN OR "135:37156" AN OR "1997:26502"/AN OR "1997:465099"/AN OR "1997:465099"/AN OR "1999:372044"/AN OR "1999:376999"/AN OR "1999:4756"/AN OR "2000:514132"/AN OR "2000:514132"/AN OR "2000:514132"/AN OR "2000:514132"/AN OR "2000:733774"/AN OR "2000:733774"/AN OR "2000:733774"/AN OR "2000:733774"/AN OR "2000:734774"/AN OR "2000:734774" L90 L106

=> d ibib abs fhit L109 1-7; d ibib abs fhit L90 1-28

L106 AND L43 L108 NOT L90

FILE=CASREACT ABB=ON FILE=CASREACT ABB=ON

SEA

21

L108 L109

134:178371 CASREACT Full-text
Synthesis and biological evaluation of highly potent analogues of epothilones B and D Altmann, K.-H.; Bold, G.; Caravatti, G.; Florsheimer, Novartis Pharma AG, TA Oncology Research, Basel, Bioorganic & Medicinal Chemistry Látters (2000), 10(24), 2765-2768 CODEN: BMCLE8; ISSN: 0960-894X COPYRIGHT 2007 ACS on STN A.; Guagnano, V.; Wartmann, M. Elsevier Science Ltd. CH-4002, L109 ANSWER 1 OF 7 CASREACT ACCESSION NUMBER: 134: CORPORATE SOURCE: PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI AUTHOR(S): TITLE: SOURCE:

SiMe2Bu-t

#### SN 10/563058 Page 108 of 172 STIC STN SEARCH RESULTS

side chains have been prepared The synthetic strategy is based on oleffin the common intermediate and allows variation of the side-chain structure in a highly convergent and stresseslective manner. These epochilone analogs, e.g. II, are more potent inhibitors of cancer cell proliferation than the corresponding parent epothilones B or D. epothilone B and D analogs incorporating fused hetero-aromatic A series of new 8

. E ...AR ===> RX(11) OF 370

W YIELD 70%

RCT AR 279226-96-9 RX(11) STAGE(1)
RGT AT 4136-95-2 2,4,6-C13C6H2COCL, AU 121-44-8 Et3N
SOL 109-99-9 THF

### SN 10/563058 Page 105 of 172 STIC STN SEARCH RESULTS

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6-18 8-19 10-20 11-21 11-22
                                                                                       10-11
                                                                                       7-8 8-9 8-19 9-10
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                                                           ring/chain bonds
                    ring/chain nodes
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Match level: 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS 1:CLASS 1:CLASS 1:CLASS 1:CLASS 1:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 17:CLASS 18:CLASS 20:CLASS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 2

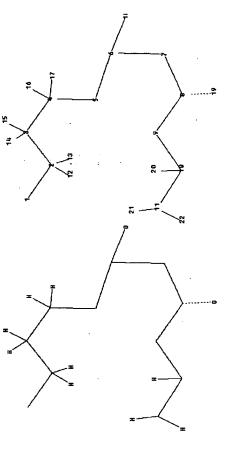
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L34 OR L35 OR L36 OR L37)
38 AND CASREACT/LC
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1/NS
4/NS
L88
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SSS FUL
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SEA FILE-REGISTRY
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SEA FILE-REGISTRY
SEA FILE-CASREACT
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          FILE=REGISTRY
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                                                                12165
2534
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                                                      50989
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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

Structure attributes must be viewed using STN Express query preparation: Uploading Ll.str

### SN 10/563058 Page 106 of 172 STIC STN SEARCH RESULTS



6-18 8-19 10-20 11-21 11-22 10-11 7-8 8-9 8-19 9-10 4-17 10-20 11-21 11-22 8-9 9-10 10-11 22 21 4-17 6-18 50 7-8 13 4-16 6-7 6-7 4-16 18 3-14 3-15 4-5 ring/chain.bonds exact/norm bonds chain nodes exact bonds chain bonds 2-12 2-13 ring/chain

Match level:
1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 7:CLASS 8:CLASS 9:CLASS 1:CLASS 1:CLASS 13:CLASS 13:CLASS 15:CLASS 15:CLASS 17:CLASS 17:CLASS 20:CLASS 20:CCAS 20:CLASS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 20:CCAS 2

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L34 560 SEA PILE=REGISTRY SSS FUL L1
L34 22933 SEA FILE=REGISTRY ABB=ON PLU=ON CCI5/ES$;
L35 27300 SEA FILE=REGISTRY ABB=ON PLU=ON CCI6/ES$
L37 726 SEA FILE=REGISTRY ABB=ON PLU=ON CCI6/ESS
L37 0 SEA FILE=REGISTRY ABB=ON PLU=ON CCI6/ESS
L38 1265 SEA FILE=REGISTRY ABB=ON PLU=ON CCI6/ESS
L39 12.65 SEA FILE=REGISTRY ABB=ON PLU=ON L39/PRO
L40 2534 SEA FILE=CASREACT ABB=ON PLU=ON L3/RRT 1
L40 65 SEA FILE=CASREACT ABB=ON PLU=ON L3/RRT 1
L42 65 SEA FILE=CASREACT ABB=ON PLU=ON L3/RRT 1
L43 55 SEA FILE=CASREACT ABB=ON PLU=ON L3/RRT 1
L43 55 SEA FILE=CASREACT ABB=ON PLU=ON L42 (L) 1/NS
L89 31 SEA FILE=CASREACT ABB=ON PLU=ON L43 (L) 1/NS
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### SN 10/563058 Page 103 of 172 STIC STN SEARCH RESULTS

```
STAGE(1)

RGT AW 1191-15-7 AlH(Bu-i)2

SOL 108-88-3 PhMe

STAGE(2)

RGT BK 7647-01-0 HCl

SOL 7732-18-5 Water, 67-56-1 MeOH

PRO BJ 226940-68-7

RX(16) RCT BL 187527-25-9

STAGE(1)
```

FGT BE 108-18-9 i-PrZNH, BF 109-72-8 BULL SOL 109-99-9 THF, 110-54-3 Hexane

STAGE(2)

RCT BJ 226840-68-7

SOL 109-99-9 THF

STAGE(3)

RGT BO 64-19-7 AcOH

SCI 109-99-9 THF

PRO BM 240815-96-7, BN 240815-97-8
REFERENCE COUNT:
60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

#### SN 10/563058 Page 104 of 172 STIC STN SEARCH RESULTS

=> file casteact FILE 'CASREACT' ENTERED AT 12:18:14 ON 11 OCT 2007 USE IS SUBJECT' OF THE TERMS OF YOUR CUSTOMER AGREEMENT COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS) Copyright of the articles to which records in this database rofer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications.

FILE CONTENT:1840 - 6 Oct 2007 VOL 147 ISS 16 New CAS Information Use Policies, enter HELP USAGETERMS for details.

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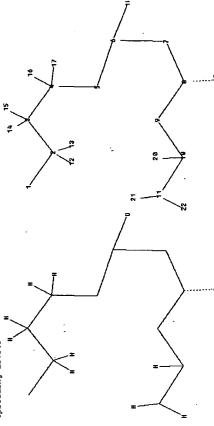
Some CASREACT records are derived from the ZIC/VINITI database (1974-1999) provided by InfoChem, INPI data prior to 1986, and Biotransformations database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

Structure attributes must be viewed using STN Express query preparation: Uploading L1.str



RX(11)

2 BL

PRO AV 240815-91-2

RX(12)

BM YIELD 39%

RX(14)

101

BN YIELD 278

#### SN 10/563058 Page 99 of 172 STIC STN SEARCH RESULTS

CAT 3144-16-9 10-CSA SOL 67-56-1 MeOH, 75-09-2 CH2C12

RGT H 87413-09-0 Martin's reagent SOL 75-09-2 CH2C12 STAGE(2)

AN 193146-27-9 (82%;97%) PRO

RCT V 185148-95-2 RX (22)

RGT X 109-72-8 BuLi, Y 108-18-9 i-PrZNH SOL 109-99-9 THF, 110-54-3 Hexane STAGE (1)

STAGE(2) RCT AN 193146-27-9 SOL 109-99-9 THF

æ

PRO BY 210690-87-2, BZ 250284-01-6

NTE stereoselective key step

REFERENCE COUNT:

82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

CASREACT L33 ANSWER 23 OF 23 ACCESSION NUMBER:

SREACT COPVRIGHT 2007 ACS on STN 131:1995355 CASREACT Full-text Total synthesis of epothlione E and related side-chain modified analoques via a Stille coupling based

strategy

Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Unkovic, S.; Hépworth, D. Department of Chamistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

CORPORATE SOURCE:

SOURCE:

AUTHOR(S):

Bioorganic & Medicinal Chemistry (1999), 7(5), 665-697 CODEN: BMECEP; ISSN: 0968-0896 Elsevier Science Ltd

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

SN 10/563058 Page 100 of 172 STIC STN SEARCH RESULTS

A Stille coupling strategy has been utilized to complete a total synthesis of epothilone E from vinyl iodide I (R1 = 1; R2 = H) and thiszolestannane II.

The central core fragment I (R1 = I; R2 = H) and its trans-isomer III (R3 = I).

The central core fragment I (R1 = SIMe2CMG3) using ring-closing metathesis (RCM), and ware.subsequently coupled to a variety of alternative stannancs to provide a library of epothilone analogs I (R1 = 2-(5-acetoxypentyl)thiszol-4-2-vinylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-furyl, 2-thienyl, Ph,3-pyridyl, CH:C(OEt)Me-(Z), RZ = H] and III [R3 = 2-(5-acetoxypentyl)thiazol-4-yl, 2-(methylthio)thiazol-4-yl, 2-piperidinothiazol-4rhiazol-5-yl, 2-(hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(fluoromethyl)thiazol-4-yl, 2-furyl, (fluoromethyl)thiazol-4-yl, 2-vinylthiazol-4-yl, 2-ethylthiazol-4-yl -4-yl, 2-piperidinothiazol-4-yl, 2-methoxythiazol-4-thiazol-4-yl, thiazol-5-yl, 2-/l, 2-methoxythiazol-4-yl, 2-ethoxythiazol-4-yl, thiazol-4-yl, thiazol-2-yl, The Stille coupling approach was then used to prepare epothilone B analogs from the key macrolactone intermediate I (R1 = 1, R2 = CH2OH) which was itself synthesized by (hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2 2-thienyl, Ph, 3-pyridyl, CH:C(OEt)Me-(Z)). nacrolactonization based strategy yl, 2-(methylthio)thiazol-4-yl, yl, 2-ethoxythiazol-4-yl, thiazol thiazol-5-yl, 2 fluoromethyl

RX(132) OF 264 COMPOSED OF RX(10), RX(11), RX(12), RX(13), RX(14), RX(15), RX(132) 
RX(132) 
AM + 2 AR + 2 AU + 2 BC + 2 BL ===> BM + BM

# SN 10/563058 Page 97 of 172 STIC STN SEARCH RESULTS

#### BY YIELD 82%

### SN 10/563058 Page 98 of 172 STIC STN SEARCH RESULTS

BZ YIELD 98

#### RCT AT 4736-60-1 RX(12)

RCT AM 210690-85-0

RX(10)

## SN 10/563058 Page 95 of 172 STIC STN SEARCH RESULTS

```
STAGE(5)
SOL 109-66-0 Pentane
PRO B 298702-07-5
NTE STEREOSELECTIVE

RX(1) RCT A 224580-52-3
STAGE(1)
RGT D 280-64-8 9-BBN
SOL 109-99-9 THF
STAGE(2)
RCT B 298702-07-5
RCT B 298702-07-5
RCT B 534-17-8 C52C03, F 603-32-7 Ph3As
CAPP-264-P Palladium, [1,1,1-bis (diphenylphosphino-cap) Representation, (SP-4-2)-
```

STAGE (3)
SOL 7732-18-5 Water
PRO C 298702-16-6
NTE STEREOSELECTIVE

68-12-2 DMF

SOL

STAGE (1)

RGT AR 7647-01-0

RX (9)

STAGE (2)

STAGE (2)

STAGE (2)

STAGE (2)

STAGE (2)

STAGE (2)

STAGE (3)

STAGE (4)

STAGE (5)

STAGE (5)

STAGE (3) SOL 75-09-2 CH2C12

PRO AQ 298702-17-7 NTE STEREOSELECTIVE RX(10) RCT AQ 298702-17-7, AS 67-56-1

STAGE(1)

RGT AV 1333-74-0 H2

CAT 109961-17-3 Ruthenium, bis[(1R)-[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine-kP]]di-µ-chlorodichhoro(N,N-diethylethanamine)di-chlorodichhoro(N,N-diethylethanamine)di-sol. 67-56-1 MeOH

STAGE(2) RGT 0 144-55-8 NaHCO3

STAGE(3) SOL 75-09-2 CH2Cl2 PRO AT 298702-18-8, AU 298702-19-9
SI THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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#### SN 10/563058 Page 96 of 172 STIC STN SEARCH RESULTS

ACCESSION NUMBER: 131:351125 CASREACT Full-text
ACCESSION NUMBER: 131:351125 CASREACT Full-text
Syntheses of (-)-epothilone B
AUTHOR(S): Schinzer, Dieter; Bauer, Armin, Schleber, Jonnifer.
CORPORATE SOURCE: Chamischer Bacter, Guernany
SOURCE: Chamischer Bacter Corporation Chamischer Bacter Corporation Chamischer Bacter Corporation Chamischer Bacter Corporation (1999), 5(9), 2492-2500 Chamischer Bacter Corporation (1999), 5(9), 2492-2500 Chamischer Corporation (1990), 5(9), 2492-2500 Chamisc

AB Two efficient routes for the total synthesis of (-)-epothilone B (I) are reported. One strategy is based on ring-closing metathesis, and a second synthesis on a macrolactonization. The key fragments are available on large scale to provide sufficient material for biol. tests. Thiszole fragment II (TBDMS = SiMe2CMe3) was obtained by an improved route starting from (S)-malic acid. The first synthesis is based on our preceding paper. The critical trisubstituted double bond C12-13 in our second approach was constructed by a highly efficient Pd-mediated coupling reaction. Ring closure was achieved by macrolactonization.

RX(79) OF 215 COMPOSED OF RX(12), RX(21), RX(10), RX(22) RX(79) 2 AT + 2 AD + 2 AP + 2 V ===> BY + BZ

water solubility, and can serve as a readily functionalizable handle to produce other useful compds. for pertinent biol. studies.

RX(33) OF 128 COMPOSED OF RX(7), RX(1), RX(9), RX(10) RX(33) 2 AG + 2 AH + 2 A + AS ====> AT + AU

PAGE 1-B

AT YIELD 428

PAGE 1-B

93

31:1

5

RGT DA 3144-16-9 10-CSA

STAGE(1)

RCT CW 210690-85-0

RX (29)

PRO RCT

RX (28)

CV 308357-81-5 CX 7558-79-4 Na2HPO4, CY 11110-52-4 Sodium amalgam CX 210690-85-0 67-56-1 MeOH, 109-99-9 THF

diastereomeric mixt.

CV 308357-81-5

PRO

#### EP 107905-52-2 ES 17455-13-9 18-Crown-6, BJ 40949-94-8 K [N(SiMe3)2] ED 218613-98-0 ES 17455-13-9 18-Crown-6, BJ 40949-94-8 K [N(SiMe3)2] 109-99-9 THF SN 10/563058 Page 91 of 172 STIC STN SEARCH RESULTS RGT AN 1191-15-7 AlH(Bu-i)2 SOL 109-99-9 THF, 142-82-5 Heptane RGT AK 12125-02-9 NH4Cl SOL 7732-18-5 Water, 60-29-7 Et20 RGT AO 304~59-6 Rochelle salt SOL 67-56-1 MeOH, 60-29-7 Et20 75-05-8 MeCN, 60-29-7 Et20 RGT CB 288-32-4 1H-Imidazole AN 1191-15-7 AlH(Bu-i)2 RGT AK 12125-02-9 NH4Cl SOL 7732-18-5 Water RGT EF 603~35-0 PPh3 SOL 75-05-8 MeCN, 60-RGT EY 7553-56-2 I2 RGT ES 17455-13-9 SOL 109-99-9 THF SOL 109-99-9 THF stereoselective EU 218614-04-1 RCT EU 218614-04-1 EX 218614-16-5 EX 218614-16-5 STAGE(2) STAGE (4) STAGE (1) STAGE (1) STAGE (3) STAGE (4) STAGE (5) STAGE (6) STAGE (5) STAGE (2) RCT RGT SOL PRO RCT RX (61) RX (55)

SN 10/563058 Page 92 of 172 STIC STN SEARCH RESULTS

SOL 67-56-1 MeOH, 75-09-2 CH2C12

D 144-55-8 NaHCO3 STAGE(2) RGT D 144-55-8 NaHCX SOL 7732-18-5 Water

CZ 210690-99-6

PRO.

CZ 210690-99-6 BF 77-7-6-9 MeAC(OMe)2 BF 313146-27-9 75-09-2 CHZC12, 110-86-1 Pyridine

PRO

RGT

RX (56)

RGT W 4111-54-0 LiN(Pr-1)2 SOL 109-99-9 THF

d 187527-25-9

RCT

RX (57)

STAGE(1)

STAGE(3) RGT AK 12125-02-9 NH4C1 SOL 7732-18-5 Water

REFERENCE COUNT:

RCT FA 193146-27-9 SOL 109-99-9 THF

STAGE (2)

```
synthesis of 12,13-desoxyapothilone B (dBpoB) has been utilized to yield an amount of dBpoP sufficient for relevant biol. studies. The results from an in vitro assay reveal that this mew analog is highly active against various tumor cell lines with a potency comparable to that of dBpoB. In particular, the growth of resistant tumor cells is inhibited by dBpoP at conces, where paclitaxel (Taxol) is basically ineffective. A preliminary assessment of its in vivo activity is also promising. The new analog, containing an addnl.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            A new epothilone analog, 12,13-desoxyapothilone F (dEpoF, 21-hydroxy-12,13-desoxyapothilone B, 21-hydroxyepothilone D), was synthesized and evaluated for
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                hydroxyl group at C21, exhibits advantages over other epothilones in terms of
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 antitumor potential. A convergent strategy employed for the semi-practical
PRO FB 193146-50-8, DB 193146-49-5
COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                Journal of Organic Chemiatry (2000), 65(20), 6525-6533 CODEN: JOCEAH; ISSN: 0022-3263
                                                                                                                                                                                                                CASREACT COPYRIGHT 2007 ACS on STN
131:266642 CASREACT FULL-CASK
Total Synthesis and Antitumor Activity of
12,13-Desoxyepothilone F: An Unexpected Solvolysis
Problem at Cl5, Madiated by Remote Substitution at C21
Lee, Chul Bom; Chou, Ting-Chao; Zhang, Xiu-Guo; Wang,
Zhi-Guang; Kuduk, Scott D.; Chappell, Mark D.;
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        Stachel, Shawn J.; Danishefsky, Samuel J.
Laboratory for Bioorganic Chemistry, The
Sloan-Kettering Institute for Cancer Research, New
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     American Chemical Society
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       York, NY, 10021, USA
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               English
                                                                                                                                                                                                                        L33 ANSWER 21 OF 23
ACCESSION NUMBER:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      CORPORATE SOURCE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    DOCUMENT TYPE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          PUBLI SHER:
                                                                                                                                                                                                                                                                                                                                                                                                                                AUTHOR(S):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  LANGUAGE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 SOURCE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     æ
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#### DB YIELD 698(80)

#### RX(52) RCT ET 188899-14-1

STEPS

2 CU

PAGE 1-A

#### SN 10/563058 Page 87 of 172 STIC STN SEARCH RESULTS

PAGE 1-B

CJ YIELD 50% OPh

#### RCT BG 188730-08-7, BH 4736-60-1 RX(15)

RGT BJ 109-72-8 Buli SOL 109-99-9 THF STAGE(1)

STAGE(2) .RGT AZ 7553-56-2 I2

STAGE(3) RGT BK 1070-89-9 (Me3S1)2N.Na

BI 210690-66-7 STEREOSELECTIVE PRO

RX (16)

BI 210690-66-7 BA 7664-39-3·HF, BB 110-86-1 Pyridine BL 312730-71-5 RCT RGT PRO SOL NTE

STEREOSELECTIVE

8

#### SN 10/563058 Page 88 of 172 STIC STN SEARCH RESULTS

BL 312730-71-5, BC 108-24-7 BE 121-44-8 Et3N, BF 1122-58-3 4-DMAP RCT RGT PRO SOL NTE RX(17)

BM 189453-18-7

STEREOSELECTIVE

RCT BV 262375-53-1, BM 189453-18-7

RX (26)

CM 280-64-8 9-BBN STAGE(1) RGT

109-99-9 THF

CM 7778-53-2 K3PO4 72287-26-4 Palladium, (1,1'-bis(diphenylphosphino-STAGE(2) CAT CAT

kP) ferrocene]dichloro-, (SP-4-2)-68-12-2 DMF, 7732-18-5 Water SOL

REFERENCE COUNT: PRO

CJ 312730-85-1 ULTRASOUND IN FIRST STAGE, STERBOSELECTIVE 42: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

CASREACT L33 ANSWER 20 OF 23 ACCESSION NUMBER:

SREACT COPYRIGHT 2007 ACS on STN 134:4795 CASREACT FULL-text Total Syntheses of Epothilones B and D . Mulser, Johann; Mantoulidis, Andreas; Oehler, Elisabeth

AUTHOR(S):

Institut fuer Organische Chemie, Universitaet Wien, CORPORATE SOURCE:

Vienna, A-1090, Austria Journal of Organic Chemistry (2000), 65(22), 7456-7467 CODEN: JOCEAH; 15SN: 0022-3263 American Chemical Society

SOURCE:

Journal DOCUMENT TYPE: PUBLI SHER:

and D are described, starting from optically pure (S)-malic acid and Mo (R)-3-hydroy-z-methylpropionate. The synthesize is highly convergent by coupling the three fragments Cl-C6 (fragment D), CJ-ClO (fragment C), and Cll-C2 (fragment B). Key steps are two sterequelective Wittig type olefinations to the microtubule stabilizing antitumor drugs epothilone B English Total syntheses of LANGUAGE: AB Tota]

generate the 12,13- and 16,17-double bonds, an enantioselective Mukaiyama aldol addition to synthesize fragment D, and a sulfone anion allyl iodide alkylation to connect fragments B and C. Finally fragment D was attached to the B + C fragment via aldol addition

RX(411) OF 711 COMPOSED OF RX(52), RX(61), RX(55), RX(28), RX(29), RX(56), + + 8 + 2 ED + 2 EP 2 ET RX(411) English

LANGUAGE:

t-BuMe2S1

achieved. Epothilones A and B were divided into fragment A (I), fragment B (II), and fragment C (III). A catalytic asym. synthesis of fragments A and B was accomplished using a catalytic asym. cyanosilytation as a key step. An enanticontrolled synthesis of fragment C was achieved in two ways. One is the use of a direct catalytic asym. aldol reaction of an unmodified ketone with an aldehyde as a key step, and the other utilizes a catalytic asym. multifunctional asym. catalysis such as'a cyanosilylation of an aldehyde, an aldol reaction of an unmodified ketone with an aldehyde, and a protonation in protonation in the conjugate addition of a thiol to an α,β-unsatd. thioester as a key step. Suzuki cross-coupling of fragment A with fragment C followed by Yamaguchi lactonization as key steps led to an enantiocontrolled synthesis of epothilone A. On the other hand, Suzuki cross-coupling of fragment B with the conjugate addition of a thiol to an  $\alpha,\beta$ -unsatd, thioester has been An enantioselective total synthesis of epothilones A and B using fragment C followed by Yamaguchi lactonization accomplished an enanticocontrolled synthesis of epothilone B.

RX(90) OF 319 COMPOSED OF RX(15), RX(16), RX(17), RX(26) RX(90) BG + BH + BC + BV ===> CJ

SN 10/563058 Page 85 of 172 STIC STN SEARCH RESULTS

STAGE(1) RGT AW 4111-54-0 LiN(Pr-1)2 SOL 109-99-9 THF STAGE(2)

RCT AS 312492-69-6 SOL 109-99-9 THF STAGE (3)

PRO AV 321522-36-5

RGT J 12125-02-9 NH4CL SOL 7732-18-5 Water

AV 321522-36-5, AX 17341-93-4 RCT

RX(13)

RGT T 110-86-1 Pyridine SOL 75-09-2 CH2C12 STAGE(1)

STAGE(2) RGT Y 144-55-8 NaHCO3 SOL 7732-18-5 Water

¥9

PRO AY 321522-37-6

RCT AY 321522-37-6 RX(14)

RGT BA 20816-12-0 0904, BB 7529-22-8 Me-morpholineoxide SOL 109-99-9 THF, 75-65-0 t-BuOH, 7732-18-5 Water STAGE(1)

STAGE (2)

RGT V 7772-98-7 Na2S203 SOL 7732-18-5 Water, 75-09-2 CH2C12

RGT C 10028-15-6 Ozone SOL 64-17-5 EtOH, 7732-18-5 Water STAGE (3)

STAGE(4) RGT Y 144-55-8 NaHCO3 SOL 7732-18-5 Water

PRO AZ 321522-38-7

134:56502 CASREACT Full-text Enantioselective Total Synthesis of Epothilones A and COPYRIGHT 2007 ACS on STN 134:56502 CASREACT L33 ANSWER 19 OF 23 ACCESSION NUMBER: TITLE:

B Using Multifunctional Asymmetric Catalysis Sawada, Dalsuke, Kanai, Motomus Shibasaki, Masakatsu Graduate School of Pharmaceutical Sciences, The University of Tokyo, Bunkyo-ku Tokyo, 113-0033, Japan Journal of the American Chemical Society (2000),

AUTHOR(S): CORPORATE SOURCE:

SOURCE:

122(43), 10521-10532 CODEN: JACSAT; ISSN: 0002-7863

American Chemical Society Journal

PUBLISHER: DOCUMENT TYPE:

86

AZ YIELD 78%

AF 321522-34-3, G 67-56-1 AH 584-08-7 K2CO3 AI 263761-11-1 RCT RGT RX (8)

SN 10/563058 Page 84 of 172 STIC STN SEARCH RESULTS

SOL 67-56-1 MeOH NTE stereoselective

RCT AI 263761-11-1

RX(19)

STAGE(1) RGT AT 1191-15-7 AlH(Bu-i)2 SOL 75-09-2 CH2C12

STAGE(2) RGT J 12125-02-9 NH4C1 SOL 7732-18-5 Water

PRO AK 263761-13-3

RCT AJ 263768-73-6 RX (9)

STAGE(1) RGT AM 109-72-8 Buli SOL 60-29-7 Et20, 109-99-9 THF, 7732-18-5 Water

STAGE(2) RCT AK 263761-13-3 SOL 109-99-9 THF

STAGE(3) RGT J 12125-02-9 NH4Cl SOL 7732-18-5 Water

PRO AL 263761-14-4

RCT AL 263761-14-4 RX (10)

STAGE(1) RGT AQ 38721-52-7 L-Selectride SOL 109-99-9 THF

STAGE(2) RCT AN 74-88-4 RGT AR 680-31-9 HMPT

STAGE(3) RGT J 12125-02-9 NH4Cl SOL 7732-18-5 Water

PRO AO 263761-15-5, AP 321522-35-4

RCT AO 263761-15-5 RX(11) STAGE(1)
RGT AT 1191-15-7 AlH(Bu-1)2
SOL 75-09-2 CH2C12

STAGE(2) RGT J 12125-02-9 NH4C1 SOL 67-56-1 MeOH, 7732-18-5 Water, 60-29-7 Et20

PRO AS 312492-69-6

RCT AU 187283-44-9 RX(12)

#### SN 10/563058 Page 81 of 172 STIC STN SEARCH RESULTS

PIELD 908

RCT AP 271792-03-1 RX (9)

RGT AQ 1070-89-9 (Me3Si) 2N.Na SOL 109-99-9 THF STAGE (1)

STAGE(2) RCT AN 279226-92-5

PRO K 279226-93-6 NTE stereoselective

RGT M 280-64-8 9-BBN SOL 109-99-9 THF RCT J 279227-12-2 STAGE (1)

RX (2)

STAGE (2)

RCT K 279226-93-6 RGT N 534-17-8 G-22CO3, O 603-32-7 Ph3As CAT 51364-51-3 Ph2-pentadienone Pd COL 68-12-2 DME

PRO L 279226-94-7

THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT stereoselective NTE st REFERENCE COUNT:

COPYRIGHT 2007 ACS on STN 133 ANSWER 18 OF 23 CASREACT ACCESSION NUMBER: 134:111 TITLE: Process

134:115799 CASREACT Full-text
Process for the production of epothilone B and
derivatives as well as intermediate products for this

process

Mulzer, Johann; Martin, Harry Schering Aktiengesellschaft, Germany PCT Int. Appl., 50 pp. INVENTOR(S): PATENT ASSIGNEE(S): SOURCE:

SN 10/563058 Page 82 of 172 STIC STN SEARCH RESULTS

CODEN: PIXXD2 Patent English FAMILY ACC. NUM. COUNT: PATENT INFORMATION: ' DOCUMENT TYPE: LANGUAGE:

KIND

PATENT NO.

§ ቒ ፰ ጛ ዿ 83 MC, PT, CH, GM, LLS, UZ, GH, BF, AT, BE, PT, SE, 1 TG 20020121 19990722 20000724 ĘŖ, ŖŢ, 20000724 GB, GR, IT, LI, LU, NL, SE, 20000724 20000724 ŊĠ, TD, JP 2001-512523 NO 2002-308 US 1999-145005P WO 2000-US20064 APPLICATION NO. WO 2000-US20064 EP 2000-948907 MR, NE, GW, ML, я, Ж, 88835888 DK, ES, FI, RO, 20030212 Ŗ, 0010201 20020731 હ AL, AM, CZ, DE, BE, CH, DE, ઠેં A2 1D, 1L,
EV, MA, 1
SE, SG,
ZA, ZW,
GM, KE,
DK, ES,
CG, CI, PRIORITY APPLN. INFO.: 8,8 WO 2001007439 WO 2001007439 JP 2003505459 NO 2002000308 EP 1226142 RW:

MARPAT 134:115799

OTHER SOURCE(S): GI

The present invention is directed to a process for the production of epochilone B compds., the improvement comprising preparing said compds. by cyclization of a compound produced from an intermediate of formula (I) wherein BG is a protecting group. 8

RX(107) OF 190 COMPOSED OF RX(8), RX(19), RX(9), RX(10), RX(11), RX(12), + ₩ RX(13), RX(14)
AF + G + AJ + AN RX(107)

### SN 10/563058 Page 79 of 172 STIC STN SEARCH RESULTS

CD 7553-56-2 I2

stereoselective CB 335160-07-1

CB 335160-07-1, BM 113453-27-3 CF 7440-66-6 Zn, CG 7440-50-8 Cu CE 335160-08-2 114221-01-3 Pd(PPh3)4 71-43-2 Benzene RCT RGT PRO CAT SOL NTE RX (32)

stereoselective

RX (33)

CE 335160-08-2 AF 3144-16-9 10-CSA CI 335160-09-3 MeoH RCT RGT PRO SOL

stereoselective

F 79-37-8 (COC1)2, Z 67-68-5 DMSO CJ 335160-10-6 CI 335160-09-3 F 79-37-8 (COC) RGT PRO SOL NTE RX (34)

stereoselective 75-09-2 CH2C12

RCT CJ 335160-10-6, AL 187283-45-0 RX (35)

STAGE(1)

RCT AM 69739-34-0 RGT AP 108-48-5 2,6-Lutidine STAGE(2)

STAGE (3) RGT AQ 584-08-7 K2CO3 SOL 67-56-1 M⊖OH

CK 335160-11-7

THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT NTE stereoselective REFERENCE COUNT: 19

CASREACT L33 ANSWER 17 OF 23 ACCESSION NUMBER:

SREACT COPYRIGHT 2007 ACS on STN 134:178371 CASREACT Full-text Synthesis and biological evaluation of highly potent

Altmann, K.-H.; Bold, G.; Caravatti, G.; Florsheimer, analogues of epothilones B and D

Novartis Pharma AG, TA Oncology Research, Basel,

CORPORATE SOURCE:

SOURCE:

AUTHOR(S):

TITLE:

Bioorganic & Medicinal Chemistry Letters (2000), 10(24), 2765-2768 CH-4002, Switz.

CODEN: BMCLE8; ISSN: 0960-894X

Elsevier Science Ltd

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

2

SN 10/563058 Page 80 of 172 STIC STN SEARCH RESULTS

A series of new epothilone B and D analogs incorporating fused hetero-aromatic side chains have been prepared. The synthetic strategy is based on olefin I as the common intermediate and allows variation of the side-chain structure in a highly convergent and stereoselective manner. These epothilone analogs, e.g. are more potent inhibitors of cancer cell proliferation than the corresponding parent epothilones B or D. 2

RX(27) OF 370 COMPOSED OF RX(9), RX(2) RX(27) AP + AM + J ===> L

Ā

#### SN 10/563058 Page 77 of 172 STIC STN SEARCH RESULTS

Wartmann, Markus; Altmann, Karl-Heinz TA Oncology Research, Novartis Pharma AG, Basel, CH-4002, Switz.

SN 10/563058 Page 78 of 172 STIC STN SEARCH RESULTS

, (CH2) 3

CORPORATE SOURCE:

SOURCE:

DOCUMENT TYPE: LANGUAGE: GI

OODEN: 69AXZT Conference; (computer optical disk) English

Proceedings of ECSOC-3, [and] Proceedings of ECSOC-4, Sept. 1-30, 1939 and 2000 (2000), Meeting Date 1999-2000, 1431-1442. Editor(9): Pombo-Villar, Esteban. Molecular Diversity Preservation International: Basel, Switz.

The authors have synthesized epothilone analogs, e.g. I, with modifications in the northern hemisphere and the heterocyclic side-chain. In all three cases the key steps for construction of the macrocyclic skeleton involve Yamaquchi macrolactonization, the build-up of the requisite seco-acid through aldol reaction between the C7-C15 aldehyde and the diamion of the O-protected C1-C6 β-hydroxy acid fragment, and the assembly of the C7-C15 aldehyde through the appropriate type of Pd(0)-catalyzed coupling reaction. The IC50 for growth inhibition of the KB-31 tumor cell line for I was 0.45 nM.

9

RX(284) OF 370 COMPOSED OF RX(29), RX(30), RX(31), RX(32), RX(33), RX(34),

**\!!!!** RX(35) Y + BX + BM + AL + AM RX (284)

CK YIELD 30%

Y 188730-08-7, BX 558-13-4 BZ 603-35-0 PPh3 BY 335160-05-9 75-09-2 CHZC12 RX (29)

BY 335160-05-9 K 109-72-8 BuLi CA 335160-06-0 RCT

RX (30)

stereoselective

stereoselective 109-99-9 THF PRO SOL NTE

STAGE(1) RGT CC 1291-32-3 ZrCp2Cl2 SOL 109-99-9 THF CA 335160-06-0 RCT

RX (31)

STAGE(2)

H

#### SN 10/563058 Page 75 of 172 STIC STN SEARCH RESULTS

A highly convergent total synthesis of the natural products epothilone B and D is described. The route is highlighted by efficient generation of a C12-C13 trisubstituted clefin I which exploits a sequential Nozaki-Hiyama-Kishi coupling and a stereoselective thionyl chloride rearrangement.

8

RX(53) OF 175 COMPOSED OF RX(6), RX(7), RX(13), RX(14) RX(53). O + N ===> AW

SN 10/563058 Page 76 of 172 STIC STN SEARCH RESULTS

PAGE 1-A

PAGE 1-B

AN YIELD 838

7719-09-7 SOC12 355009-08-4 o **355009-06-2** U 7719-09-7 SO RCT RGT PRO SOL RX (6)

60-29-7 Et20, 109-66-0 Pentane

Y 22560-16-3 Superhydride X 210690-99-6 RGT PRO SOL NIE

T 355009-08-4

RX (7)

other product detected 109-99-9 THF

RX(13)

X 210690-99-6 AC 26299-14-9 PCC ' AM 193146-27-9 RGT RGT

N 187527-25-9, AM 193146-27-9 AO 4111-54-0 LiN(Pr-1)2 AN 193146-49-5

RX (14)

stereoselective, other product detected, no exptl.
37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT RCT N RGT AO PRO AN NTE ST REFERENCE

CASREACT L33 ANSWER 16 OF 23 ACCESSION NUMBER: TITLE:

SREACT COPYRIGHT 2007 ACS on STN
134:311010 CASREACT Full-text
Synthetic epothilone analogs with modifications in the northern hemisphere and the heterocyclic side-criain-synthesis and biological evaluation End, Nicole; Bold, Guido; Caravatti, Glorgio;

AUTHOR(S):

73

PRO AM 298702-16-6

š. .

## SN 10/563058 Page 73 of 172 STIC STIN SEARCH RESULTS

SN 10/563058 Page 74 of 172 STIC STN SEARCH RESULTS

NTE STEREOSELECTIVE

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Department of Chemistry & Blochemistry, University of Notre Dame, Notre Dame, IN, 46556-5670, USA Organic Letters (2001), 3114), 2221-2224 CODEN: ORLEF7; ISSN: 1523-7060 American Chemical Society
                                                                                                                                                                                                                                                                                            STACE(1)
RGT AS 7647-01-0 HCl
CAT 109361-17-3 Ruthenlum, bis[(IR)-[1,1'-binaphthalene]-2,2'-
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                135:180642 CASREACT Full-text Fotal Synthesis of Epothilones B.and D
                                                                                                                                                                                                                                                                                                                                                  diylbis[diphenylphosphine-kP]]di-µ-
chlorodichloro(N,N-diethylethanamine)di-
SOL 67-56-1 MeOH
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         REACT COPYRIGHT 2007 ACS on STN 135:180642 CASREACT Full-text
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              Taylor, Richard E.; Chen, Yue
                                                                                                                                                                                                                                                            RCT AR 298702-17-7, AT 67-56-1
                                                                                                        STAGE(2)
RGT N 144-55-8 NaHCO3
                                                                                                                                                                                                                                                                                                                                                                                                                                                                  STAGE(3)
RGT N 144-55-8 NaHCO3
                                     STAGE(1)
RGT AS 7647-01-0 HC1
SOL 67-56-1 MeOH
                                                                                                                                                                                                                                                                                                                                                                                                                   STAGE(2)
RGT AV 1333-74-0 H2
                                                                                                                                                          STAGE(3)
SOL 75-09-2 CH2Cl2
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         STAGE(4)
SOL 75-09-2 CH2C12
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     English
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         L33 ANSWER 15 OF 23 CASREACT ACCESSION NUMBER: 135:18
                                                                                                                                                                                                         PRO AR 298702-17-7
NTE STEREOSELECTIVE
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         PRO AU 298702-19-9
NTE STEREOSELECTIVE
RCT AM 298702-16-6
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              AUTHOR(S):
CORPORATE SOURCE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              PUBLI SHER:
DOCUMENT TYPE:
LANGUAGE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  SOURCE:
                                                                                                                                                                                                                                                              RX(10)
     RX (9)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       1) - RCT AB 298702-07-5 RGT AO 603-32-7 Ph3As, AP 534-17-8 Cs2CO3 CAT 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-
                                                     PAGE 1-B
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           κP) ferrocene]dichloro-, (SP-4-2)-
SOL 68-12-2 DMF
                                                                                                                                                                                                                                                                                                                                                                                                                                STAGE(3)
RGT AE 1070-89-9 (Me3Si)2N.Na
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     RGT AN 280-64-8 9-BBN SOL 109-99-9 THF
                                                                                                                                                                                                                                                                                                       RGT AC 109-72-8 BuLi
SOL 109-99-9 THE
                                                                                                                                                                                                                                                                                                                                                            STAGE(2)
RGT AD 7553-56-2 I2
SOL 109-99-9 THF
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  STAGE(3)
SOL 7732-18-5 Water
                                                                                                                                                                                                                                                                                                                                                                                                                                                                              STAGE(4)
RCT AA 298702-12-2
SOL 109-99-9 THF
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  STAGE(5)
RGT D 64-19-7 AcOH
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                STAGE(4)
SOL 60-29-7 Et20
                                                                                                                                                                                                                                         RCT Z 4736-60-1
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   AB 298702-07-5
STEREOSELECTIVE
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     RCT AL 224580-52-3
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     STAGE (1)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         STAGE (2)
                                                                                                                                                     AU 428
                                                                                                                                                                                                                                                          RX (6)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       RX (8)
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### SN 10/563058 Page 71 of 172 STIC STN SEARCH RESULTS

ACCESSION NUMBER: 135:226826 CASREACT Full-text
Synchesis of epothliones, intermediates and analogs for use in treatment of cancers with multidrug resistant phenotype of cancers with multidrug resistant phenotype. 17, Lee, Chul Bom; Chappell, Mark; Stachel, Shawn; Chou, Ting-chao Source: Sloan-Kettering Institute for Cancer Research, USA POT Int. Appl., 234 pp. Coben: PIXXD2 POCUMENT TYPE: PACT INT. Appl., 234 pp. Coben: PIXXD2 PACHAILY ACC. NUM. COUNT: 5 PATENT INFORMATION:

多类异岛美 # 3 Ρ, LS, UZ, FR, GB, GR, IT, LI, LU, NL, SE, MC, MK, CY, AL, TR £, £, ER, US, BE, SE, TG 20010301 20010301 20010301 gr, rk, ug, AT, PT, ď, SK, JP 2001-563492 US 2000-185968P US 2000-250447P WO 2001-US6643 CA 2001-2401800 EP 2001-916335 APPLICATION NO. WO 2001-US6643 12, N K2, B, R, 品系 ¥, 13, 13, Ą SL, Ge, EE, TM, MARPAT 135:226826 Z ¥ ₩ Z Z 8,8,8 ES, RO, 20010907 SE, SE, 20021127 £ 8 5 20010907 DATE DK, FI, IS, MG, SK, ₩. F. EI, Ē 3 ĕä ť SI, KIND Ā BE, CH, SI, LT, ŝ JP 2004500388 PRIORITY APPLN. INFO.: R, RG, G, G R: AT, BE, WO 2001064650 WO 2001064650 OTHER SOURCE(S): CA 2401800 EP 1259490 表 3 G S 单 B E, PATENT NO. RW:

[R1 (W) m] q - CY

Me

Me

Me

Me

Me

Me

Me

The OR2

AB The present invention provides convergent processes for preparing epothilones, desoxyepothilones, and analogs, e.g., I [M = NH, O; CY = aryl, heteroaryl; q = 1-5; W = absent, NH, CO, CS, O, S, C(V)2; V = H, halogen, OH, SH, maino, (un)substituted alkyl, heteroalkyl, aryl, heteroaryl; m = 1-5; bond W···Rl =

### SN 10/563058 Page 72 of 172 STIC STN SEARCH RESULTS

single bond, double bond; RI = OR, SR, NR2; CO2R, CONHR, N3, N2, N2R; halogen, un(substituted) cyclic or acyclic aliphatic, heteroaliph, aryl or heteroaryl, polymer, carbohydrate; R = H, un(substituted) cyclic or acyclic aliphatic, heteroaliph, aryl or heteroaryl, polymer, carbohydrate; R = H, un(substituted) cyclic or acyclic bencaryl; R4; R5 = H, un(substituted) cyclic or acyclic aliphatic, heteroaryl, acyl, heteroaryl, acyl, aroyl, acyl, aryl or heteroaryl, optionally substituted by one or more of OH, alkoxy, carboxy, carboxyl, optionally substituted by one or more of OH, alkoxy, carboxy, carboxyl, PR3, R3, R4, N2, N2R, cyclic or acyclic aliphatic, aryl, heteroaryl; Z = O, N(ORE), NNFRG; RE, RF, RG = un(substituted) cyclic or acyclic aliphatic; n = O-31, for the troatment of cancer. Biol. activities of novel compds. based on I and mothods for the treatment of cancer and cancer which has developed a multi-drug phenotype are presented. Thus, 21-oxo-12,13-deatoypethilone B and 15-azeapothilone B were active vs leukemia CCRF-CEM cells (ICSO = 0.027 µM; ICSO = 0.021 µM, resp.).

RX(112) OF 295 COMPOSED OF RX(8), RX(8), RX(9), RX(10) RX(112) Z + AA + AL + AL = AB = AD

### SN 10/563058 Page 69 of 172 STIC STN SEARCH RESULTS

Preparation of epothilone intermediates Vite, Gregory D.; Kim, Soong-Hoon; Hoeefle, Gerhard Bristol-Myers Squibb Company, USA 135:287591 CASREACT Full-text PCT Int. Appl., 28 pp. CODEN: PIXXD2 Patent INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: ACCESSION NUMBER: DOCUMENT TYPE:

English

FAMILY ACC. NUM. COUNT: PATENT INFORMATION: LANGUAGE:

CA, CH, CN, GE, GH, CM, IK, IR, IS, PL, PT, RO, UG, US, UZ, AT, BE, CH, CY, PT, SE, TR, BF, 20010319 20030528 20010319 20010323 20000324 DATE ZW, NL, SN, US 2003-447082 US 2000-191975P US 2001-811808 APPLICATION NO. WO 2001-US9620 US 2001-811808 AS 20020523 , AL, AM, AT, AU. E 20030715 20011004 KIND DATE EI, FR, CI, SQ, B2 A1 US 2002042109 E US 6593115 E US 2004023345 E PRIORITY APPIN. INFO.: WO 2001073103 PATENT NO. RW:

MARPAT 135:287591 OTHER SOURCE(S):

æ

containing a carboxyl group which is esterified, the hydroxyl groups on the moiety protected and the resulting compound oxidized by, e.g. ozone, to form a first intermediate. The first intermediate can be reacted with a enzymically degrading certain epothilone compds. to form ring-open structures The present invention relates to a process for the preparation of intermediates useful in the synthesis of epothilone analogs by initially position 1 which is subsequently hydrolyzed to form a triphenylphosphine adduct to

: G VIII 11 4 + O... RX(4) OF 31

### SN 10/563058 Page 70 of 172 STIC STN SEARCH RESULTS

OMe

PIELD 558

#### RCT 0 190369-98-3 RX (4)

STAGE (1)

RGT R 1070-89-9 (Me3Si) 2N.Na SOL 109-99-9 THF RCT P 364336-83-4 SOL 109-99-9 THF STAGE(2)

PRO Q 364336-77-6

; <u>.</u> .

L33 ANSWER 14 OF 23 CASREACT COPYRIGHT 2007 ACS on STN

EP YIELD 86%

RCT AB 370578-43-1 RX (6) STAGE(1) RGT AD 121-44-8 Et3N SOL 75-09-2 CH2C12

RGT AE 7719-09-7 SOC12 SOL 75-09-2 CH2C12 STAGE(2)

STAGE(3) RGT G 7732-18-5 Water

STAGE(4) RGT AF 429-41-4 Bu4N.F SOL 109-99-9 THF

AC 370578-22-6 stereoselective PRO

RCT AC 370578-22-6, EM 994-30-9

RX (64)

RGT AD 121-44-8 Et3N CAT 1122-58-3 4-DMAP SOL 75-09-2 CH2C12 STAGE(1)

RGT D 144-55-8 NAHCO3 SOL 7732-18-5 Water

STAGE(2)

PRO DL 370578-62-4

RCT DL 370578-62-4 RX (32)

STAGE(1)

SN 10/563058 Page 68 of 172 STIC STN SEARCH RESULTS

RGT CK 7529-22-8 Me-morpholineoxide SOL 75-65-0 t-BuOH, 109-99-9 THF, 7732-18-5 Water

STAGE(2) CAT 20816-12-0 0504 SOL 7732-18-5 Water

STAGE(3) RGT DN 7631-90-5 NaHSO3

STAGE(4) RGT DO 546-67-8 Pb(OAc)4 SOL 141-78-6 ACOEt

PRO DM 342607-03-8

RX (33)

STAGE(1) RGT AU 4111-54-0 LiN(Pr-i)2 SOL 109-99-9 THF DQ 219990-08-6 RCT

STAGE(2) RCT DM 342607-03-8 SOL 109-99-9 THF

STAGE (3)

RGT AA 12125-02-9 NH4C1 SOL 7732-18-5 Water

DR 342607-02-7 in-situ generated reagent, stereoselective

DR 342607-02-7, FO 17341-93-4 E 110-86-1 Pyridine EO 342607-17-4 75-09-2 CHZC12 RCT RGT PRO SOL RX (66)

EO 342607-17-4 RCI RX (45)

STAGE(1)
RGT CK 7529-22-8 Me-morpholineoxide SOL 75-65-0 t-BuOH, 109-99-9 THF, 7732-18-5 Water

CAT 20816-12-0 0s04 STAGE (2)

STAGE (3)

RGT DN 7631-90-5 NaHSO3

STAGE(4) RGT DO 546-67-8 Pb(OAC)4 SOL 141-78-6 ACOEt

THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT PRO EP 342607-35-6 66 REFERENCE COUNT:

L33 ANSWER 13 OF 23 CASREACT COPYRIGHT 2007 ACS on STN

### SN 10/563058 Page 65 of 172 STIC STN SEARCH RESULTS

RGT Z 109-72-8 BuLi SOL 109-99-9 THF STAGE(2)

STAGE(3)
RGT CJ 37342-97-5 Hydrozirconocene Cl SOL 109-99-9 THF

RGT CK 7553-56-2 I2 SOL 109-99-9 THF STAGE (4)

CH 335160-07-1 PRO

AO 113453-27-3, CH 335160-07-1 RCT RX (30)

GM 12621-78-2 Zinc alloy, base, Zn,Cu 14221-01-3 Pd(PPh3)4 71-43-2 Benzene STAGE (1)

Sol

STAGE(2) RGT BY 3144-16-9 10-CSA SOL 67-56-1 MeOH

RGT BL 67-68-5 DMSO, AB 79-37-8 (COC1)2 SOL 75-09-2 GHZC12 STAGE(3)

PRO CL 335160-10-6

RCT H 187283-45-0, CL 335160-10-6 RX(31)

STAGE(1) RGT BT 4111-54-0 LiN(Pr-i)2

STAGE(2)

RCT F 69739-34-0 RGT BW 108-48-5 2,6-Lutidine

AGE (3) RGT CQ 584-08-7 K2CO3 SOL 67-56-1 MGOH STAGE (3)

PRO CP REFERENCE COUNT:

THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT CP **335160-11-7** 

COPYRIGHT 2007 ACS on STN CASREACT

L33 ANSWER 12 OF 23 ACCESSION NUMBER: TITLE:

135:331283 CASREACT Full-text
Stereoselective Syntheses of Epothliones A and B via
Nitrile oxide Cycloadditions and Related Studies
Note of Parties of English Carreira, Erick M.
Laboratorium fuer Organische Chemie, ETH-Zuerich, AUTHOR(S): CORPORATE SOURCE:

Zurich, CH-8092, Switz.
Journal of Organic Chemistry (2001), 66(19), 6410-6424
CODEN: JOCEAH; ISSN: 0022-3263

American Chemical Society

SOURCE:

Journal PUBLISHER: DOCUMENT TYPE:

SN 10/563058 Page 66 of 172 STIC STN SEARCH RESULTS English

LANGUAGE: GI

The expedient and fully stereocontrolled synthesis of epothilones A (I; R = H) and B I (R = Me) are described. The routes described make extensive study of nitrile oxide cycloaddns. as surrogates for aldol addition reactions and have led to the realization of a highly convergent synthesis based on the Kanemasa hydroxyl-directed nitrile oxide cycloaddn. As well, our synthetic efforts have led to the development of new reaction methodologies and served as the proving ground for several modern methods for asym. carbon-carbon bond B

RX(451) OF 751 COMPOSED OF RX(6), RX(64), RX(32), RX(33), RX(66), RX(45) RX(451) AB + EM + DQ + FO ===> EP

ΑB

*;*~

65

#### SN 10/563058 Page 63 of 172 STIC STN SEARCH RESULTS

SOL 109-99-9 THF

BR 186692-68-2 stereoselective

RX (28)

AX 461044-35-9, BR 186692-68-2 BW 603-32-7 Ph3As, BX 534-17-8 Cs2CO3, BY 280-64-8 9-BBN BV 461044-42-8 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-RCT RGT PRO CAT

NTE

kP)ferrocenejdichloro-, (SP-4-2)stereoselective, regioselective

54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS
T: RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT REFERENCE COUNT:

SREACT COPYRIGHT 2007 ACS on STN 136:318824 CASREACT FULL-text 136:318824 CASREACT FULL-text 5 Synthetic and semisynthetic analogs of epothilones: chemistry and biological activity CASREACT L33 ANSWER 11 OF 23 ACCESSION NUMBER:

TITLE:

AUTHOR(S):

Alaman, Karl-Heinz; Blommers, Marcel J. J.; Caravatti, Giorgio; Florsheimer, Andreas; Nicolaou, Kyriacos C.; O'Reilly, Terrence; Schmidt, Alfred;

Schinzer, Dieter; Wartmann, Markus

TA Oncology Research, Novartis Pharma AG, Basel, CH-4002, Switz. CORPORATE SOURCE:

ACS Symposium Series (2001), 796(Anticancer Agents), 112-130

SOURCE:

CODEN: ACSMC8; ISSN: 0097-6156 American Chemical Society

this paper we present the synthesis of these analogs and we discuss the impact of such modifications on tubulin polymerization activity as well as vivo, we have investigated a series of structural modifications involving the epoxide site (C12/C13) and the heterocyclic side-chain of epothilones. In which exhibit potent in vitro antiproliferative activity. Epothilone B is a 3 30-fold more potent inhibitor of human cancer cell growth than paclitaxel in paclitaxel-sensitive cancer cell lines and in paclitaxel-reasistant lines exceeds paclitaxel activity by 102 - 103-fold. In addition, epothilone B models. In order to gain a better understanding of the structural requirements for epothilone—mediated cytotoxicity and antitumor activity and Epothilones A and B are naturally occurring microtubule depolymn. inhibitors, to discover analogs with similar potency but perhaps better tolerability in English cytotoxicity in vitro. PUBLISHER: DOCUMENT TYPE: LANGUAGE: AB Epothilones

RX(146) OF 320 COMPOSED OF RX(29), RX(30), RX(31) RX(146) BK + CG + AC + H + F ===> CP

#### SN 10/563058 Page 64 of 172 STIC STN SEARCH RESULTS

Q

#### RCT BK 188730-08-7, CG 558-13-4 RX (29)

STAGE(1) RGT CI 603-35-0 PPh3 SOL' 75-09-2 CH2C12

#### SN 10/563058 Page 61 of 172 STIC STN SEARCH RESULTS

of novel pyranose synthons. The utility of this very convergent and effective method is demonstrated by the concise total synthesis of epothilones. The stereoselective I-catalyzed aldol condensation of acetaldehyde with (25)-3-hydroxy-2-methylpropanal gave 2,4-dideoxy-4-methyl-L-erythro-pentopyranose. propenyl)-L-xylonic acid 6-lactone. This compound was a chiral synthon needed for the total synthesis of epothilone C [(45,7R,8S,9S,13Z,16S)-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-Oxidation of the latter gave 2,4-dideoxy-4-methyl-L-three-pentonic acid  $\delta$ -lactone. Alkylation of the  $\delta$ -lactone gave 2,4-dideoxy-4-methyl-2-(2thiazolyl)ethenyl]oxacyclohexadec-13-ene-2,6-dione]

RX(172) OF 316 COMPOSED OF RX(23), RX(24), RX(25), RX(26), RX(27), RX(28) RX(172) BC + BH + BN + BQ + AX ===> BV

ΑX

#### SN 10/563058 Page 62 of 172 STIC STN SEARCH RESULTS

BV YIELD 65% -OBn-t

PAGE 1-B

109-63-7 BF3-Et20 461044-38-2 BC 247900-97-6 RX (23)

7732-18-5 Water, 75-05-8 MeCN

BE 461044-38-2, BH 109-80-8 BI 461044-39-3 7550-45-0 TIC14 RCT PRO CAT RX (24)

RX (25)

BI 461044-39-3 BL 79-37-8 (COCL)2, BM 67-68-5 DMSO BK 461044-40-6 RGT PRO PRO

BK 461044-40-6, BN 184246-51-3 AR 109-72-8 BuLi BO 461044-41-7 109-99-9 THF RCT RGT PRO SOL

RX (26)

stereoselective

Bo 461044-41-7 RCT RX(27) STAGE(1).
RGT BS 7616-83-3 Hg(ClO4)2, BT 471-34-1 CaCC3
SOL 109-99-9 THF, 7732-18-5 Water

STAGE(2) RCT BQ 29949-93-7 RGT V 680-31-9 HMPT, BU 1070-89-9 (Me3Si)2N.Na

61

### SN 10/563058 Page 59 of 172 STIC STN SEARCH RESULTS

PAGE 1-B

BU YIELD 638 1 OMe

BF 188730-08-7, BH 558-13-4 603-35-0 PPh3 335160-05-9 RX(18)

L 335160-06-0 109-99-9 THF, 110-54-3 Hexane BI 335160-05-9 AJ 109-72-8 BuLi RX(19)

SUBSTAGE(1) 10 minutes, 18 - 23 deg C SUBSTAGE(2) 1 hour, room temperature 75-09-2 CH2C12 RGT PRO SOL SOL

RCT RGT PRO SOL

SN 10/563058 Page 60 of 172 STIC STN SEARCH RESULTS

CON SUBSTAGE(1) room temperature -> -75 deg C SUBSTAGE(2) 30 minutes SUBSTAGE(3) 1 hour, -75 deg C SUBSTAGE(4) 1 hour, room temperature

L 335160-06-0 RCT

RX (3)

STAGE(1)

RGT N 37342-97-5 Hydrozirconocene Cl SOL 109-99-9 THF CON SUBSTAGE(1) room temperature SUBSTAGE(2) 30 minutes, room temperature

STAGE(2)
RGT O 7553-56-2 I2
CON SUBSTAGE(1) 10 minutes, 20 - 25 deg C
SUBSTAGE(2) 10 minutes

stereoselective PRO M 335160-07-1 NTE stereoselectiv

RCT CW 279227-12-2 RX (39)

4 hours, room temperature DB 280-64-8 9-BBN 109-99-9 THF STAGE(1) SOL SOL SON

M 335160-07-1 STAGE (2)

DC 603-32-7 Ph3As, DD 534-17-8 Cs2CO3 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-SUBSTAGE(1) room temperature -> -10 deg C SUBSTAGE(2) -10 deg C -> room temperature SUBSTAGE(3) 24 hours, room temperature KP)ferrocene]dichloro-, (SP-4-2)-7732-18-5 Water, 68-12-2 DMF S SOL RGT CAT

BU 501691-10-7 PRO BUREFERENCE COUNT:

THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 20

CASREACT . COPYRIGHT 2007 ACS on STN L33 ANSWER 10 OF 23 ACCESSION NUMBER:

137:247231 CASREACT Full-text
Aldolass-catalyzed asymmetric synthesis of novel
epychiones synthons as a new entry to heterocycles and
epychilones Liu, Junjie; Wong, Chi-Huey AUTHOR(S): CORPORATE SOURCE: TITLE:

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

Angewandte Chemie, International Edition (2002), 41(8), 1404-1407 CODEN: ACIEFS; ISSN: 1433-7851 SOURCE:

Wiley-VCH Verlag GmbH DOCUMENT TYPE: LANGUAGE: PUBLI SHER: В

Enzymic reactions catalyzed by DERA (2-deoxyribose-5-phosphate aldolase, deoxyriboaldolase, (1)) provide the basis for a new strategy for the synthesis

PAGE 1-B

BO YIELD 938

RCT T 193146-30-4D RX (27)

15 minutes, room temperature BY 1070-89-9 (Me3Si)2N.Na 109-99-9 THF STAGE(1) RGT B SOL 1

2

RCT BP 346652-91-3 CON 15 minutes, -78 deg C -> -40 deg C STAGE (2)

PRO BC NTE so REFERENCE COUNT:

BQ 583829-96-3 solid-supported reaction 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS NT: RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

138:237914 CASREACT Full-text The total synthesis and biological assessment of CASREACT COPYRIGHT 2007 ACS on STN 138:237914 CASREACT L33 ANSWER 9 OF 23 ACCESSION NUMBER: TITLE:

trang-epothilone A Altmann, Karl-Heinz; Bold, Guido; Caravatti, Giorgio; Denni, Donatienne; Florsheimer, Andreas; Schmidt, Alfred; Rihs, Grety; Wartmann, Markus HelVetica Chimica Acta (2002), 85(11), 4086-4110 CODEN: HCACAV; ISSN: 0018-019X Corporate Research, Novartis Pharma AG, Switz. CORPORATE SOURCE:

AUTHOR(S):

SOURCE:

Verlag Helvetica Chimica Acta Journal English DOCUMENT TYPE: LANGUAGE: PUBLI SHER:

SN 10/563058 Page 58 of 172 STIC STN SEARCH RESULTS

two different convergent strategies. In a first-generation approach, construction of the C(II)-C(I2) bond by PdO-catalyzed Negabia-type coupling between the C(I2)-to-C(I3) trans-vinyl iodide II and the C(7)-to-C(I3) alkyl iodide III preceded the (nonselective) formation of the C(6)-C(7) bond by aldol reaction between the C(7)-to-C(I3) aldehyde and the dianion derived from the C(1)-to-C(I5) aldehyde and the dianion derived from the C(1)-to-C(I6), acid IV. The lack of selectivity, in the aldol step was addressed in a second-generation approach, which involved construction of the C(6)-C(7) bond in a highly diastereoselective fashion through reaction between The total synthesis of (125,135)-trans-epothilone A (1) was achieved based on cancer cell lines in vitro. In contrast, the biol. activity of V is at least two orders of magnitude lower than that of VI or I. the acetonide-protected C(1)-to-C(6) diol ("Schinzer's ketone") and the C(7)-to-C(11) aldehyde. As part of this strategy, the C(11)-C(12) bond was established subsequent to the critical aldol step and was based on B-alkyl Suzuki coupling between the C(1)-to-C(11) fragment and C(12)-to-C(15) transvinyl iodide II. Both approaches converged at the stage of the 3-0, 7-0-bisepoxidn. of the trans C(12)-C(13) bond could be achieved by epoxidn. with Oxone in the presence of the catalyst 1,2:4,5-di-0-isopropylidene-L-erythro-TBS-protected seco acid, which was converted to trans-deoxyepothilone A via Yamaguchi macrolactonization and subsequent deprotection. Stereoselective I is at least equipotent with natural epothilone A (VI) in its ability to induce tubulin polymerization and to inhibit the growth of human (12R,13R)-epoxide isomer (V) in 27% yield (54% based on recovered starting 2,3-hexodiuro-2,6-pyranose, which provided a 8:1 mixture of I and its The absolute configuration of I was established by X-ray crystallog.

RX(123) OF 496 COMPOSED OF RX(18), RX(19), RX(3), RX(39) RX(123) BF + BH + CM ===> BU

27

25

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RGT CF 280-64-8 9-BBN SOL 109-59-9 THF CON SUBSTAGE(1) room temperature SUBSTAGE(2) 3 hours, room temperature

STAGE(2) RGT E 7732-18-5 Water CON room temperature

CON room temperature STAGE(3)

RCT CA 186692-68-2
RGT CG 603-32-7 Ph3As, CH 534-17-8 Cs2CO3
CAT 72287-26-4 Palladium, [1,1'-bis (diphenylphosphino-kP) ferrocene]dichloro-, (SP-4-2)SOL 68-12-2 DMF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 2 minutes, room temperature

SUBSTAGE(3) room temperature SUBSTAGE(4) 8 hours, room temperature STAGE(4)

RGT BS 12125-02-9 NH4C1 SOL 7732-18-5 Water CON room temperature

#### PRO CE 461044-42-8

ACCESSION NUMBER: A total synthesis of epothilones using solid-supported reagents and scavengers Storer, R. Ian, Takemoto, Toshiyasu, Jackson, Philip Storer, R. Ian, Takemoto, Toshiyasu, Jackson, Philip Storer, R. Ian, Takemoto, Toshiyasu, Jackson, Philip S.; Ley, Steven V. University of Cambridge, Cambridge, Cambridge, Cambridge, Cambridge, Cambridge, Cambridge, Cambridge, Caps 180, UK Angewandte Chemie, International Edition (2003), April Miley-VCH Verlag GmbH & Co. KGeA BOOUNGET TYPE: English GI

#### SN 10/563058 Page 56 of 172 STIC STN SEARCH RESULTS

AB A total synthesis of epothilone C (I) with concomitant formal synthesis of epothilone A is described, using immobilized reagents and scavengers to effect multistep synthetic transformations and purifications.

 $RX(27) OF 210 \dots T + BP ===> BQ.$ 

T solid supporte d

PAGE 1-A

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STEPS
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PAGE 1-B
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CE YIELD 658 →OBu-t

RCT AG 247900-97-6, AI 109-80-8 RX (9)

SOL 75-09-2 CH2C12
SOL 75-09-2 CH2C12
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) room temperature
SUBSTAGE(4) 30 minutes STAGE (1)

RGT J 144-55-8 NaHCO3 SOL 7732-18-5 Water STAGE(2)

PRO AJ 461044-39-3

STAGE (1)

RX (25)

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KGT BV 79-37-8 (COC1)2 SOL 75-09-2 CH2C12, 67-68-5 DMSO CON SUBSTAGE(2) 30 minutes

STAGE(2) RCT AJ 461044-39-3 SOL 75-09-2 CHZC12 CON SUBSTAGE(2). 3 hours

STAGE(3) RGT AE 121-44-8 Et3N

PRO: BU 461044-40-6

RCT BX 184246-51-3 RX (26) STAGE(1)
RGT BF 109-72-8 BuLi
SOL 109-99-9 THF
CON SUBSTAGE(2) 15 minutes

STAGE(2)
RCT BU 461044-40-6
CON SUBSTAGE(2) room temperature

STAGE(3) RGT BS 12125-02-9 NH4Cl SOL 7732-18-5 Water

PRO BY 461044-41-7

RCT BY 461044-41-7

RX (27)

STAGE(1)

RGT CB 7616-83-3 Hg(CLO4)2, CC 471-34-1 CaCO3
SOL 7732-18-5 Water
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 2 hours, room temperature

STAGE(2)
SOL :60-29-7 Et20
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 10 minutes, room temperature

BZ 3020-28-8 BG 680-31-9 HMPT, CD 1070-89-9 (Me3Si)2N.Na 109-99-9 THF SUBSTAGE(3) room temperature SUBSTAGE(4) 1 hour SOL

STAGE(4) RGT BS 12125-02-9 NH4Cl SOL 7732-18-5 Water

RCT BT 461044-35-9

RX(28)

PRO CA 186692-68-2

STAGE (1)

23

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RCT . AS 863981-49-1 RX (14)

AU 64-17-5 EtOH 24057-28-1 Pyridinium tosylate 64-17-5 EtOH 65 deg C STAGE (1) SOL SOL

Q 79-37-8 (COC1)2, AV 67-68-5 DMSO 75-09-2 CH2C12 -78 deg C STAGE (2) SOL SOL NO

AW 121-44-8 Et3N -78 deg C -> room temperature STAGE (3) RGT 80N

AT 688318-68-5 Swern oxidn. in stage 2 PRO

RCT AY 185148-95-2 RX(15)

RGT BA 4111-54-0 LiN(Pr-i)2 CON -78 deg C STAGE(1)

STAGE(2) RCT AT 688318-68-5 CON -78 deg C

#### PRO AZ 688318-69-6

THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT stereoselective NTE st REFERENCE COUNT:

Synthesis of atorvastain and epothilone synthons via 2-deoxyribose-5-phosphate aldolase-catalyzed ssymmetric aldol condensation of aldehydes Wong, Chi-huey; Liu, Junjie; De Santis, Grace; Burk, EACT COPYRIGHT 2007 ACS on STN 139:277113 CASREACT Full-text L33 ANSWER 7 OF 23 CASREACT ACCESSION NUMBER: 139: INVENTOR(S): TITLE:

The Scripps Research Institute, USA; Diversa Mark PATENT ASSIGNEE (S):

PCT Int. Appl., 63 pp CODEN: PIXXD2 Corporation SOURCE:

English Patent LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

DOCUMENT TYPE:

DATE APPLICATION NO. DATE . KIND PATENT NO.

3 £ £ £ 9 K 8 9 20030314 6 6 3 g 82, KZ, NO, BY, FI, KR, WO 2003-US7982 ES, 호호 ŘΕ, KG, X ¥22,8 AZ, IS, 20040401 AT, AU, DE, DK, IL, IN, MA, MD, 20030925 ¥ 8 ₹ **6** AE, AG, GR, GM, HR, LT, LT, WO 2003077868 WO 2003077868

5

#### STIC STN SEARCH RESULTS SN 10/563058 Page 52 of 172

, 21 ES, ВХ, PT, ŢŢ, AZ, EE, SK, TD, S, X 20060705 TR, 20030314 GB, GR, IT, LI, LU, NL, SE, CY, AL, TR, BC, CZ, EE, HU, 20030314 20030314 20030314 Ĭ, Ä, US 2006-481653 US 2002-364641P US 2003-390544 WO 2003-US7982 CA 2003-2479247 AU 2003-225810 US 2003-390544 EP 2003-744689 JP 2003-575922 SK, SL, TJ, ZM, ZW Š ð AT, BE, BG, IT, LU, MC, GA, GN, GO, SE, YU, SD, ĸ, Ķ 20031218 20041215 DK, ES, SD, MX, 20030929 20070118 20050714 ŠĆ, 끉뫂 UA, UG, US, UZ, V GH, GM, KE, LS, N KG, KZ, MD, RU, 1 F1, FR, GB, GR, H BF, BJ, CF, CG, C CH, DE, L LT, LV, F T 20 Y. JP 2005520510 US 2007015260 PRIORITY APPIN. INFO.: F, 5, £ BE, CA 2479247 AU 2003225810 US 2003232416 EP 1485498 R: AT, RW:

MARPAT 139:277113 OTHER SOURCE(S): 2

acceptor aldehydes. The reaction products typically contain at least two new stereogenic centers and can be produced in enantionerically pure form. As such, DERA catalyzed asym. aldol chemical can be exploited to produce synthons for the synthesis of a variety of bioactive mols., e.g. epothilone A. catalyze sequential asym. aldol reactions between a wide variety of donor and The present invention is based on the discovery that 2-decayribose-5-phosphate aldolase (DERA, EC 4.1.2.4) and variants thereof can be used to

RX(147) OF 294 COMPOSED OF RX(9), RX(25), RX(26), RX(27), RX(28) RX(147) AG + AI + BX + BZ + BI ===> CE

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B

An efficient synthesis of the epothilone B derivative 26-fluoroepothilone B (I) was realized by early introduction of the synthetically demanding fluoromethyl epoxide function. The presence of a fluoro substituent results in a remarkable increase in the stability of the epoxide, which tolerates the wide range of reaction conditions required for the fragment coupling step and game transformations.

RX(175) OF 310 COMPOSED OF RX(10), RX(24), RX(25), RX(26), RX(27), RX(14), RX(175) H + AG + BW + AY ===> AE

STEPS

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AZ YIELD 778

RX (24)

RX (25)

RX (26)

SOL CON NTE

RX(27)

4

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EI YIELD 938

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SUBSTAGE(1) room temperature
SUBSTAGE(2) 18 hours, 90 deg C
SUBSTAGE(3) 90 deg C -> room temperature
attachment to solid-supported reagent Fluka polymer bound triphenylphosphine N 193146-30-4 O 603-35-0D PPh3 EB 725738-64-7D 108-88-3 PhMe NTE RGT PRO SOL RX (50)

#### EB 725738-64-7D RCT RX(54)

SUBSTAGE(1). room temperature SUBSTAGE(2) 10 minutes, room temperature SUBSTAGE(3) room temperature -> -78 deg C CY 1070-89-9 (Me3Si)2N.Na 109-99-9 THE STAGE(1) SOL SOL SON

EH 346652-91-3 SUBSTAGE(1) 1 minute, -78 deg C SUBSTAGE(2) 10 minutes, -78 deg C STAGE (2) 8 5 5 8

PRO EI 583829-56-3

NTE solid-supported reactant

NTE solid-supported THERE ARE 122 CITED REFERENCES AVAILABLE FOR THERE ARE 122 CITED REFERENCES AVAILABLE IN THE RE FORWAT

AREACT COPYRIGHT 2007 ACS on STN 140:423500 CASREACT FULL-text Total synthesis of 26-fluoro-epothilone B rath-Heinz Novertis Institutes for Blomudical Research, Basel, 4002, Switz. Synlett (2004), (4), 693-697 CODEN: SYNLES; ISSN: 0936-5214 GGOOTG Thieme Verlag Journal English L33 ANSWER 6 OF 23 CASREACT ACCESSION NUMBER: 140:4: AUTHOR(S): CORPORATE SOURCE: PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI SOURCE:

PAGE 1-B

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<u>@</u>

ÄE

AF YIELD 868

RCT AE 823203-10-7 RX (6)

SOL 109-99-9 THF CON 23 deg C -> 0 deg C STAGE (1)

RCT AG 1070-89-9 (Me3Si)2N.Na SOL 109-99-9 THF CON 0 deg C STAGE (2)

STAGE (3)

7. AB 822203-08-3 109-99-9 THF 4 SUBSTAGE(1) 0 deg C SUBSTAGE(2) 0 deg C -> 23 deg SUBSTAGE(3) 5 hours, 23 deg C

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STAGE(4) RGT R 12125-02-9 NH4C1 SOL 7732-18-5 Water CON 23 deg C

AF 823203-09-4

1 last stage quench
THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT PRO AF NTE las REFERENCE COUNT:

EACT COPYRIGHT 2007 ACS on STN 141:140221 CASREACT Full-text Multi-step application of immobilized reagents and CASREACT L33 ANSWER 5 OF 23 ACCESSION NUMBER: TITLE:

scavengers: A total synthesis of epothilone C Storer, R. Ian, Takemoto, Toshiyasu; Jackson, Philip S.; Brown, Dearg S.; Baxendale, Ian R.; Ley, Steven V. Department of Chemistry, University of Cambridge, CORPORATE SOURCE:

Chemistry -- A European Journal (2004), 10(10), Cambridge, CB2 1EW, UK

2529-2547

SOURCE:

CODEN: CEUJED; ISSN: 0947-6539 Wiley-VCH Verlag GmbH & Co. KGAA

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

A stereoselective convergent synthetic strategy was applied, incorporating polymer-supported reagents, catalysts, serventy and catch-and-release techniques to avoid frequent aqueous work-up and chromatog, purification The enanticselective preparation of 3 key fragments heptanone I, (S)-2-methyl-6-heptenal, and thiazole II along with their elaboration via diastereoselective coupling into epothilone C is presented. The total synthesis of the cytotoxic antitumor natural product epothilone C has provided a stage for the exploitation and further development of æ

RX(112) OF 662 COMPOSED OF RX(50), RX(54) RX(112) N + EH ===> EL

4

8

ă.H

AUTHOR(S):

## SN 10/563058 Page 43 of 172 STIC STN SEARCH RESULTS PRO CA 861125-00-0

L33 ANSWER 4 OF 23 CASREACT COPPRIGHT 2007 ACS on STN
ACCESSION NUMBER: 142:113814 CASREACT Full-text
TITLE: Method for producing Cl-C15 fregments of epothilones and derivatives thereof
INVENTOR(S): Studila, Wenner Schering Aktenia, Wenner Schering Aktenia, Wenner Schering Aktenia, Wenner PATENT ASSIGNEE(S): PCT Int. Appl., 48 pp.
DOCUMENT TYPE: CODEN: PIXXD2 PCT Int. Appl., 48 pp.
DOCUMENT TYPE: Construction COUNT: 1
PATENT INFORMATION:

APPLICATION NO. DATE	WO 2004-EP6685 20040619	BA, BB, BG, BR, BW, BY, BZ, CA,	DZ, EC, EE, EG, ES, FI, GB, GD,	IS, JP, KE, KG, KP, KR, KZ, LC,	MG, MK, MN, MW, MX, MZ,	RU, SC, SD, SE, SG, SK, SL, SY,	US, UZ, VC, VN, YU, ZA, ZM, ZW	NA, SD, SL, SZ, TZ, UG, ZM, ZW,	IM, AT, BE, BG, CH, CY, CZ, DE,	IE, IT, LU, MC, NL,	CI, CM, GA, GN, GO, GW, ML, MR,		DE 2003-10331004 20030703	AU 2004-254200 20040619	CA 2004-2531078 20040619	EP 2004-740122 20040619	B	, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR	CN 2004-80019005 20040619	BR 2004-12179 20040619	IN 2006-DN56 20060103	72	NO 2006-554 20060202	US 2006-563058 20060619	DE 2003-10331004 20030703	WO 2004-EP6685 20040619	
KIND DATE APPL	20050113	AL, AM, AT, AU, AZ, BA	CR, CU, CZ, DK, DM, DZ,	HR, HU, ID, IL, IN, IS,	LT, LU, LV, MA, MD, MG,	PG, PH, PL, PT, RO, RU,	TR, TI, TZ, UA, UG, US,	GM, KE, LS, MW, MZ, NA,	KG, KZ, MD, RU, TJ, TM,	FI, FR, GB, GR, HU, IE,	TR, BF, BJ, CF, CG, CI,	-	A1 20050224	20050113 AU	A1 20050113 CA 2	A1 20060405 EP 2	CH, DE, DK, ES, FR, GB,	LT, LV, FI, RO, MK, CY,	A 20060809 CN 2		A 20070824 IN	A 20060427 MX			: DE	. WO	
PATENT NO.	WO 2005003071	W: AE, AG,			LR, LS,					EE, ES,			DE 10331004	AU 2004254200	CA 2531078	EP 1641734	R: AT, BE,	IE, SI,	CN 1816514	BR 2004012179	IN 2006DN00056	MX 2006PA00172	NO 2006000554	US 2007142675	PRIORITY APPLN. INFO.		

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The invention relates to a method for preparing C1-C15 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1aR1b = (GH2)m; m = 2 - 5; R2a, R2b = H, C1-10-alkyl, C2-10-alkynl, aryl, C7-20-aralkyl; R2aR2b = (GH2)n; n = 2 - 5; R3 = H, C1r10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = H, C1r10-alkyl, aryl, C7-20-aralkyl; R4aR4b = (GH2)p; p = 2 - 5; R3 = H, C1r10-alkyl, aryl, C7-20-aralkyl; R6, R7 = H; R6R7 = bond, O; G = X:CR8, bi- or tricyclic aryl; R8 = H, halogen, (un)substituted C1-20-alkyl, aryl, C7-20aralkyl; x = 0, (OR23)2, C2-10-alkylene-α,ω-dioxy, H(OR9), CR10R11; R23 = C1-20-alkyl; R9 = H, protecting group; R10, R11 = H, C1-10-alkyl, aryl; C7-20-aralkyl; CR10R11 = 5 - to 7-membered carbocycle; R13 = CH2OR13a, CH2-halo, PGI4)CRZaRZbC(:Z)CRIARIbCHRI4CH2R13 [PG = H, protecting group], which is then treated with a Cl3-Cl5 fragment, G-CRZO'CH2CHR7'R21 [R7' = H; R20' = halogen, N3, NHR29, OH, O-PG, NR29-PG, Cl-20-(perfluoro)alkylsulfonyloxy, (Cl-4-alkyl), deisopropylidenation/detetrahydropy ranylation with catalytic 4-MeC6H4SO3H in active ingredients II [AK = OC(:0), OCH2, CH2C(:0), NR29C(:0), NR29SO2; R29 = H, CI-6-alkyl] according to known methods. The invention also relates to the intermediate product I. Thus, I [Ria = Rib = R5 = Me, R2a = CH2CH:CH2-B, R2b  $\beta$ , R20 = OSiMe2CMe3- $\alpha$ , G = 2-methylbenzothiazol-5- y1, PG = SiMe2CMe3, Z = O) was prepared from (S)-4-(2-methyl-3-oxohept-6-en- 2-y1)-2,2-dimethyl-1,3-= R4b = H- $\alpha$ , R3 = H- $\beta$ , R4a = Me- $\beta$ , R6R7 = bond, R13 = CO2H, R14 = OSIMe2CMe3-EtOH, silylation with CF3SO2SiMe2CMe3, regioselective desilylation with (t)-camphor-10- sulfonic acid, Swern oxidation with DMSO/(COC1)2 in CH2C12 and carbonyl oxidation with NaOC12 in aqueous THF/Me3COH. The produced C1-C15 NO2, Cl, Br-substituted) benzyloxy, NR29SO2Me, NR29C(:0)Me, CH2C(:0)Me, R21 OH, halo, O-PG, P+Ph3Hal- (Hal = F, Cl, Br, I), P(0)(0Q)2 (Q = Cl-10-alkyl, Ph), P(:0)Ph2; R29 = H, Cl-6-alkyl), to form the Cl-Cl5 epothilone catalytic tetrapropylammonium perruthenate, Wittig reaction with [(3S)-3-(2butyldimethyleilyl)oxylheptanal, tetrahydropyranylation, desilylation with BudNF in THF, oxidation in CH2C12 containing N-methylmorpholine N-oxide and CHO, COZRIJD, CO-halo, Rija, Ri4a = H, SOZalkyl, SOZ-aryl, SOZ-aralkyl; RijaRi4a = (CH2)o, CRI5aRi5b; o = 2 - 4; Ri3b, Ri4b = H, CI-10-alkyl, aryl, C7-20-aralkyl; Ri5a, Ri5b = H, CI-10-alkyl, aryl, C7-20-aralkyl; Ri5a, Ri5b = H, CI-10-alkyl, aryl, C7-20-aralkyl; Ri5aRi5b = (CH2)q; q = 3 - 6; R20 = 0-P6, NRR29, NR32 Z = 0, H(OR1Z); Ri2 = H, PG of epothilones and derive. The procedure comprises the bonding of a CI-C6 fragment, Ri3CH2CHRI4CRIaRibC(:0)CHR2aR2b, to a C7-C12 fragment, RSC(:V) (CH2)3CR4aR4bC(:W)R3a [V, W = O, (OR23)2, C2-10-alkylana- a, a-dioxy, H(OR9)], to form a C1-C12 fragment, RSC(:V) (CH2)3CR4aR4bCR3a(0carbonyl oxidation with NaOC12 in aqueous THF/Me3COH. The produced C1-C15 epothilone intermediate products can be converted into the intrinsically dioxane via lithiation and reaction with (2S,6RS)-2-methyl-6-[(tert- yl)propyl]triphenylphosphonium iodide corresponding C1-C12 fragments methylbenzothiazol-5

RX(6) OF 60 ... AE + AB ===> AE

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CA YIELD 318

#### RCT AV 861124-76-7 RX (22)

BV 1070-89-9 (Me3Si)2N.Na 109-99-9 THF STAGE(2) RCT BS 190370-00-4 SOL 109-99-9° THF CON 12 hours, -20 deg C 15 minutes, 0 deg C

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STAGE(3) RGT M 12125-02-9 NH4Cl SOL 7732-18-5 Water

RCT BU 861124-92-7 RX (23)

PRO BU 861124-92-7

STAGE(1)

RGT BX 3144-16-9 10-CSA

SOL 67-56-1 MeOH, 73-09-2 CH2C12

CON SUBSTRAGE(1) 5 minutes, 0 deg C

SUBSTRAGE(2) 0.5 hours, 0 deg C

SUBSTRAGE(3) 1 hour, 25 deg C

STAGE(2) RGT BI 121-44-8 Et3N

PRO BW 861124-94-9

RCT BW 861124-94-9 RX (24) STAGE(1)
RGT BZ 26412-87-3 Pyridine-SO3 (1:1), BO 67-68-5 DWSO, BI 121-44-8 Et3N
SOL 75-09-2 CHZO12
CON 0.5 hours, 25 deg C

RGT M 12125-02-9 NH4Cl SOL 7732-18-5 Water, 60-29-7 Et20 STAGE(2)

PRO BY 861124-97-2

RCT S 187283-45-0, BY 861124-97-2 RX (25) STAGE(1)
RGT BZ 26412-87-3 Pyridine-SO3 (1:1), BO 67-68-5 DMSO, BI
121-44-8 Ec3N
SOL 75-09-2 CHZC12
CON 0.5 hours, 25 deg C

STAGE(2) RGT M 12125-02-9 NH4Cl SOL 7732-18-5 Water, 60-29-7 Et20

STAGE(3) RCT J 69739-34-0 RGT L 108-48-5 2,6-Lutidine SOL 75-09-2 CH2012 CON 2 hours, 0 deg C

STAGE(4) RGT BE 7647-01-0 HCl SOL 7732-18-5 Water

STAGE(5) RGT CB 584-08-7 K2CO3 CON 15 minutes, 25 deg C

# SN 10/563058 Page 39 of 172 STIC STN SEARCH RESULTS CON SUBSTACE(1) 5 deg C SUBSTACE(2) 1 minute, 5 deg C

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Ar 67-68-5 DMSO, BH 79-37-8 (OCL)2
75-09-2 CA2CL2
78-08-75 (1) -78 deg C
SUBSTAGE(1) -78 minutes, -78 deg C
                                                                                                                                                                                                                                                                                                                                                                                                                                               SUBSTAGE(1) -70 deg C
SUBSTAGE(2) 10 minutes, -70 deg C
SUBSTAGE(3) 1 hour, -30 deg C
SUBSTAGE(3) 1 hour, -30 deg C
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 109-99-9 THF
SUBSTAGE(1) 30 minutes, -70 deg C
SUBSTAGE(2) 3.5 hours, -70 deg C
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        -70 deg C
-70 deg C
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            SUBSTAGE(1) -70 deg C
SUBSTAGE(2) 10 minutes,
SUBSTAGE(3) 15 minutes,
                                                                                                                                                                                                                                                                                                                                                                                                                        BL 4111-54-0 LiN(Pr-i)2
109-99-9 THF
                                                                                                                                                                                                                                                          BF 279225-51-6
75-09-2 CH2C12
30 minutes, -78 deg C
                                                                                                                                                                                                                                                                                                                   AG 121-44-8 Et3N
-78 deg C -> -10 deg
                                                                                                                               2 hours, room temperature
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      AL 7646-85-7 ZnC12
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      BG 279226-52-7
            T 220775-18-8
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   109-99-9 THF
                                                                                                                                                                                                                                                                                                                                                      BG 279226-52-7
Wittig reaction
                                                         BD 924727-13-9
                                                                                BD 924727-13-9
BF 279226-51-6
                                                                                                                                                                                                                                                                                                                                                                                        RCT BI 305840-13-5
                                                                                                      104-15-4 TsOH
64-17-5 EtOH
                                    5 hours
                                                                                                                                                                                                                                                                                                                                                                                                                STAGE(1)
STAGE(2)
RCT T
SOL 1
                                                                                                                                                                            STAGE(1)
RGT A
SOL 7
CON S
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            STAGE(2)
RGT 1
SOL 1
                                                                                                                                                                                                                                                   STAGE (2)
                                                                                                                                                                                                                                                                                                          STAGE(3)
                                                                                                                                                                                                                                                                                                                     RG1
SON
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             STAGE (3)
                                                                                                                                                                                                                                                            SOL
SOL
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CAT
SOL
SOL
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                                                                                   RX(16)
                                                                                                                                                      RX(17)
                                                                                                                                                                                                                                                                                                                                                                                         RX(18)
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#### SN 10/563058 Page 40 of 172 STIC STN SEARCH RESULTS

RCT BJ 69739-34-0

PRO BK 924727-14-0 REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:172686 CASREACT Full-text
New method for totally synthesizing natural product-epothilones Yan, Jiaqi Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, 29 pp. ODDEN: CHXEV Patent Chinese 20021205 20021205 CN 2002-153675 CN 2002-153675 APPLICATION NO. 20030521 DATE KIND 4 FAMILY ACC. NUM. COUNT: PATENT INFORMATION: CM 1418881 PRIORITY APPIN. INFO.: PATENT NO. PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE: INVENTOR (S): LANGUAGE:

AB The invention discloses a novel multi-step synthetic method for preparing Epothilions A and epothilione B (I; R = H or Me resp.) in a convergent approach starting from 2.2-dimethyl-2-acceptantal, propionaldehyde SAMP hydrazone, and Et 2-methylthiazolidin-4-ylcarboxylate.

RX(97) OF 191 COMPOSED OF RX(22), RX(24), RX(25) RX(97) AV + BS + S + J ===> CA \$

33

STAGE (4)

### SN 10/563058 Page 37 of 172 STIC STN SEARCH RESULTS

STAGE(2)

RCT P 865535-39-3 RGT V 534-17-8 Cs2CO3 CAT 603-32-7 Ph3As, 72287-26-4 Palladium,

bis(diphenylphosphino-kP)ferrocene]dichloro-,

20L 80N

 $68-12-2~\mathrm{DMF}$  2 hours, 0 deg C -> room temperature

T 865535-59-7 PRO T 865535-59-7 RCT RX(11)

AQ 1310-65-2 LiOH AP 865535-60-0

7.732-18-5 Water, 67-63-0 Me2CHOH
2.5 hours, 60 deg C
1: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT PRO AP SOL 77, CON 2.

L33 ANSWER 2 OF 23 CASREACT ACCESSION NUMBER: 146:2 TITLE: Total

NEACT COPYRIGHT 2007 ACS on STN 146:22907 OCKSEACT Pull-text 140:12919 synthesis and antitumor activity of ZK-EPO: The first fully synthetic epothilone in clinical

development

Klar, Ulrich, Buchmann, Bernd; Schwede, Wolfgang; Skuballa, Werner; Hoffmann, Jens; Lichtner, Rosemarie

AUTHOR(S):

Schering AG, Research Center Eurpoe, Berlin, Germany Angewandte Chemie, International Edition (2006), 45(47), 7942-7948
CODEN: ACIEFS; ISSN: 1433-7851
Wiley-VCH Verlag GmbH & Co. KGaA
English CORPORATE SOURCE: SOURCE:

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

efficacy than taxanes, such as paclitaxel and second-generation epothilones, fast and efficient cellular uptake, no recognition by efflux mechanisms, and an improved therapeutic window. From about 350 active epothilone analogs synthesized by a highly convergent synthesis,  $ZK-EPO\ (I)$  was chosen for clin. development on the basis of its nosen for clin, development on the basis of its This compound exhibits higher activity and outstanding preclin. data. Ŗ

#### SN 10/563058 Page 38 of 172 STIC STN SEARCH RESULTS

RX(84) OF 314 COMPOSED OF RX(15), RX(16), RX(17), RX(18) RX(84) BC + T + BI + BJ ===> BR

BK YIELD 738

RCT BC 823203-10-7 RX(15)

RGT BE 1070-89-9 (Me3Si)2N.Na SOL 109-99-9 THF STAGE (1)

37

# SN 10/563058 Page 35 of 172 STIC STN SEARCH RESULTS

100.0% DONE 3173 VERIFIED SEARCH TIME: 00.00.04

468 HIT RXNS

23 DOCS

=> d ibib abs fhit L33 1-23

COPYRIGHT 2007 ACS on STN L33 ANSWER 1 OF 23 CASREACT ACCESSION NUMBER: 146:2 TITLE:

146:251631 CASREACT Full-text
Total synthesis and biological assessment of benzimidazole-based analogs of epothilone A:

Ambivalent effects on cancer cell growth inhibition Cachoux, Frederic; Isarno, Thomas; Wartmann, Markus; Altmann, Karl-Heinz growth inhibition

Prostwick Chemical, Illkirch, Fr. ChemBiochem (2006), 7(1), 54-57 CODEN: CBCHFK; ISSN: 1439-4227 Wiley-VCH Verlag GmbH 6 Co. KGaA

CORPORATE SOURCE: SOURCE:

AUTHOR(S):

Journal English

DOCUMENT TYPE: LANGUAGE: GI

PUBLI SHER:

The title (12R,13S)- and (12S,13S)-epoxy-benzimidazole epothilone derivs. (R12 =  $\beta$ -,  $\alpha$ -H, resp.), as well as the corresponding (12Z)- and (12E)- $\Delta$ 12-olefin epoxide precursors, were prepared and evaluated for inhibition of growth of human cancer cell lines, such as KB-31 and KB-8511. æ

RX(30) OF 64 COMPOSED OF RX(10), RX(3), RX(4), RX(11) RX(30) AN + AC + S ====> AP

AC

SN 10/563058 Page 36 of 172 STIC STN SEARCH RESULTS

RCT AN 3020-28-8 RX(10)

15 minutes, room temperature RGT AO 1070-89-9 (Me3Si)2N.Ne SOL 109-99-9 THF CON 15 minutes, room temporation STAGE(1)

RCT AC 279226-82-3 CON 30 minutes, -78 deg C STAGE (2)

O 865535-38-2 stereoselective, Wittig reaction PRO

RX (3)

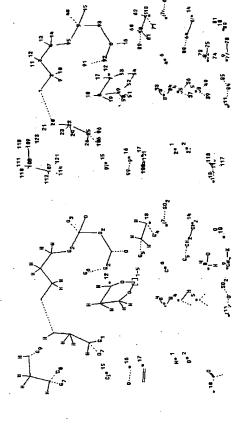
O 865535-38-2 Q 3144-16-9 10-C\$A P 865535-39-3 G7-56-1 MeOH, 75-09-2 CH2C12 RGT PRO SOL SOL

17 hours, room temperature S 279227-12-2 RG RX (4)

STAGE(1) RGT U 280-64-8 9-BBN SGL 109-99-9 THF CON 90 minutes, room temperature

35

# SN 10/563058 Page 33 of 172 STIC STN SEARCH RESULTS



25-96 25-106, 35-37 38-39 38-40 49-52 52-54; 53-54 58-89 59-71 23 24 25 26 27 28 68 71 72 73 74 75 96 97 101 106 107 108 109 110 111 112 9-50 49-51 58-59 58-60 58-61 58-89 59-62 59-71 64-65 64-88 67-68 3-4 4-95 5-93 5-48 5-15 5-95 6-92 6-16 6-93 7-8 7-53 8-80-81 83-84 84-85 91-92 100-101 107-108 107-112 107-114 107-8-18 8-19 20-21 20-22 22-23 22-24 22-25 25-26 25-96 25-106 2-3 2-9 2-10 3-4 3-11 3-12 4-14 4-13 4-95 5-93 5-48 5-15 5-95 18 19 21 22 3 62 64 65 67 109-123 115-116 116-117 116-118 98 99 100 17 61 15 35-37 38-39 38-40 98-99 8-49 49-52 52-54 53-54 13 14 1 1 58 59 40 93 39 11 12 1 50 51 95 20 35 37 38 89 91 121 123 10 chain nodes: 115 22-25 67-68 80-81 hain bonds

### SN 10/563058 Page 34 of 172 STIC STN SEARCH RESULTS

7-17 8-18 8-19 20-21 22-23 22-24 25-26 58-59 58-60 58-61 59-62 64-65 72-73 72-74 07-108 107-112 108-109 108-110 108-111 109-113 2-9 2-10 3-11 3-12 4-14 4-13 32-33 32-34 35-36 49-50 49-51 77-78 100-101 exact bonds :

61:[\*1],[\*2]

G2:[+3];[+4],[+5]

G3:H,[+6]

G4:X,OH,O,[+7]

G5:[\*8],[\*9],[\*10],[\*11]

G6: (\*12], [\*13], [\*14]

G7:[\*15],[\*16],[\*17]

39:0, P, X

38:0, N, X, [\*18]

23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 40:CLASS 65:CLASS 67:CLASS 68:CLASS 71:CLASS 72:CLASS 73:CLASS 100:CLASS 109:CLASS 110:CLASS 111:CLASS (112:CLASS 113:CLASS 52:Atom 53:Atom 54:Atom 58:CLASS 59:CLASS ASS 6:CLASS 7:CLASS 8:CLASS 14:CLASS 15:CLASS 16:CLASS 1 36:CLASS 37:CLASS 38:CLASS 39:CLASS 85:CLASS 95:CLASS 96:CLASS 97:Atom 98:CLASS 99:CLASS 81:CLASS 83:CLASS 84:CLASS 22:CLASS 35:CLASS 80:CLASS 51:CLASS

118:CLASS 121:CLASS 123:CLASS #

: Unsaturated ype of Ring System

fragments assigned product role: containing 1

fragments assigned reactant/reagent role: containing 107

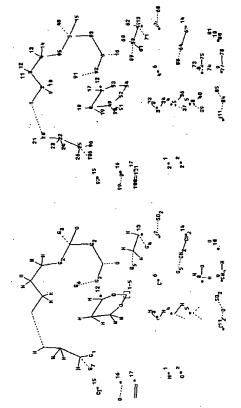
468 REACTIONS) 23 SEA FILE=CASREACT SUB=L30 SSS FUL L31 (

133

83-84 84-85 91-92 98-99 107-114 107-121 109-123 115-116 116-

# SN 10/563058 Page 31 of 172 STIC STN SEARCH RESULTS

Structure attributes must be viewed using STN Express query  $p_{\ell}$ eparation: Uploading Lib.str



7-17 8-18 8-19 20-21 20-22 22-23 22-24 22-25 25-26 25-96 25-106 2-3 2-9 2-10 3-4 3-11 3-12 4-14 4-13 4-95 5-93 5-48 5-15 5-95 hain bonds

19-50 49-51 58-59 58-60 58-61 58-89 59-62 59-71 64-65 64-88 67-68

80-81 83-84 84-85 91-92 100-101

ing/chain bonds

35-37 38-39 38-40 98-99

1-20 2-3 3-4 4-95 5-93 5-48 5-15 5-95 6-92 6-16 6-93 7-8 7-53 8-49 49-52 52-54 53-54 xact/norm bonds

22-25 25-96 25-106 35-37 38-39 38-40 49-52 52-54 53-54 58-89 59-71

83-84 84-85 91-92 98-99

2-9 2-10 3-11 3-12 4-14 4-13 7-17 8-18 8-19 20-21 22-23 22-24 25-26 32-33 32-34 35-36 49-50 49-51 58-59 58-60 58-61 59-62 64-65 72-73 72-74

31

### SN 10/563058 Page 32 of 172 STIC STN SEARCH RESULTS

77-78 100-101

G1:{\*1],[\*2}

G2:(\*3),[\*4],[\*5]

G3:H,[+6]

G4:X,OH,O,[+7]

G5:[\*8],[\*9],[\*10],[\*11]

G6:[\*12],[\*13],[\*14]

67:[\*15],[\*16],[\*17]

CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLAS: 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 67:CLASS 68:CLASS 71:CLASS 72:CLASS 73:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 88:CLASS 95:CLASS 96:CLASS 97:Atom 98:CLASS 99:CLASS 100:CLASS 52:Atom 53:Atom 54:Atom 58:CLASS 59:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS 83:CLASS 84:CLASS 85:CLASS 81:CLASS 35:CLASS 80:CLASS 65:CLASS 51:CLASS 101:CLASS 32: CLASS

Seneric attributes :

Saturation Type of Ring System

: Unsaturated : Polycyclic

560 SEA FILE=REGISTRY SSS FUL L1 69 SEA FILE=CASREACT ABB=ON PLU=ON L3 STR និខិន \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

Structure attributes must be viewed using STN Express query preparation: Uploading L31b.str

# SN 10/563058 Page 29 of 172 STIC STN SEARCH RESULTS

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US 2003144523	A1 . 2	20030731	S	2000-485292	5292		20000503
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		_	g	WO 1998-EP5064	5064	3	19980810
OTHER SOURCE(S):	CASREACT	CASREACT 130:168162; MARPAT 130:168162	Σ	RPAT 1	30:168162		

E 5

8

Compds. I (R1 = H, OH, OR7; R2 = H, protective group; R3, R4 = H, C1-10-alkyl, C7-10-aralkyl; R3R4 = (GH2)m; R5, R6 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R7 Wittig (R§ = CH:CH2, RIO = CHO), hydroboration and oxidation of hexenol IV [R§ = CH:CH2, RIO = CH(OH) GIZRS] with N-methylmorpholine N-oxide/TPAP and oxidation of keto aldehyde IV (R9 = CHZCH), RIO = COCH2RS) to keto acid IV (R9 = CH2COZH, RIO = COCHZRS) or hexenol IV [R9 = CH:CHZ, RIO = CH(OH)CHZRS] can be oxidized then alkylated with LiN(GH0e2)2 and R6Z (Z = leaving group) and the = C1-20-alkyl, C7-20-aralkyl; R1 ≠ OH, when R2 = SiMe2CMe3, R3 = R4 = R5 = Me, R6 = H), useful for the preparation of epothilone and epothilone derivs., are prepared from (R)-, (S)- or (1)-pantolactone (II, R8 = H) via tetrahydropyranylation with 3,4-dihydro-2H-pyran and pyridinium percentanylation with 3,4-dihydro-2H-pyran and pyridinium percentanylation of rHe ether II (R8 = THP) with DIBAL-H, Witti reaction of lactol III with MORPHSPHE-/Buli, oxidation of pentenol IV (R9 = CH:CH2, R10 = CH2CH) with (COCOL)2/DWSO in CH2CL2, addition of an organometallic compound, R5CH2Y (Y = Li, MgX, X = Cl, Br, I), to aldehyde IV = CH:CH2, R10 = COCHR5R6), can hydroborated and oxidized as above, leading to resulting ketone IV (R9

### SN 10/563058 Page 30 of 172 STIC STN SEARCH RESULTS

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HIGHEST RN 950149-06-1 HIGHEST RN 950149-06-1 10 OCT 2007 10 OCT 2007 STRUCTURE FILE UPDATES: DICTIONARY FILE UPDATES: New CAS Information Use Policies, enter HELP USAGETERMS for details.

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FILE CONTENT:1840 - 6 Oct 2007 VOL 147 ISS 16

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now has more than 13.8 million reactions CASREACT Some CASREACT records are derived from the ZIC/VINITI database (1974-1999) provided by InfoChem, INPI data prior to 1986, and Biotransformations database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

27

# SN 10/563058 Page 27 of 172 STIC STN SEARCH RESULTS

protecting group; R11 = H, protecting group] including all the stereoisomers and their mixts. are prepared E.g., title compound (S)-III [R5 = R6 = Me, R9 = R11 = H, R10 = TBDPS] was prepared in 6 steps from D-(-)-pantolactone via reaction with 3,4-dihydro-ZH-pyran, hydride reduction, Wittig reaction with methyltriphenylphosphonium bromide, protection of OH with TBDPS-C1, detetrahydropyranyl, and reduction with borane-THF.

New (C13-C15)-fragments, method for their preparation and their application for synthesis of epothilone and Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; CAPLUS COPYRIGHT 2007 ACS on STN 1999:116658 CAPLUS Full-text Schirner, Michael Schering A.-G., Germany. Ger. Offen., 14 pp. epothilone derivatives CODEN: GWXXBX 130:168163 German FAMILY ACC. NUM. COUNT: L102 ANSWER 23 OF 24 PATENT ASSIGNEE(S): PATENT INFORMATION: ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR (S): SOURCE:

19970809 19980810 19980810 DE, DK, ES, CF, CG, CI, 19980810 19980810 TT, UA, UG, SE, MC, PT, 19980810 19980810 20000503 19970809 19970809 19971024 S & S DATE £ 3 7 # ¥ £ N. CASREACT 130:168163; MARPAT 130:168163 DE 1997-19735575 CA 1998-2299608 WO 1998-EP5064 JP 2000-506196
AT 1998-946309
US 2000-485592
DE 1997-19735574
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DE 1997-1974892E
DE 1997-1974892E
DE 1997-1974892E
DE 1997-1974892E
WO 1998-EP5064 BE, CH, SE, BF, #**₹** GR, IT, LI, LU, MK APPLICATION NO. AU 1998-93409 EP 1998-946309 UG, ZW, AT, MC, NL, PT, SN, TD, TG SK, AD, 8 ¥ ES, FR, RO, CY, 20010828 20070815 20030731 82, E, នូម្ព 20000607 20070725 19990211 9990218 9990218 .999030 SE, SD, ₩, Ä,E ĭĕ, KIND A2 A2 A3 음. 8,5,5,8,8 유. PRIORITY APPLN. INFO.: R: AT, BE, IE, SI, JP 2001512723 AT 368036 US 2003144523 DE 19735575 CA 2299608 WO 9907692 WO 9907692 OTHER SOURCE(S): GI 1005465 PATENT NO. 9893409 E E S

### SN 10/563058 Page 28 of 172 STIC STN SEARCH RESULTS

AB The title compds. [1; II; R1 = H, alkyl, aryl, aralkyl; R2 = H, protecting group; R3 = CH, halo, OR6; R6 = protecting group; R4 = H, alkyl; R5 = H, alkyl, aryl, aralkyl] are prepared E.g., title compound I [R1 = Me, R2 = TBDPS, R3 = TBDMS] was prepared in 6 steps from L-(-)-malk acid via cyclization, 3-O-protection of 3(S)-hydroxy-2-tetrahydrofuranone, hydride reduction, into goaning and chain lengthaning, 1-O-protection of 3(S)-(tert-butyldiphenylsilyloxy)-1,4-paranedial, and oxidation of 3(S)-(tert-butyldiphenylsilyloxy)-5-(tert-butyldimethylsilyloxy)-2- pentanol. This was further treated with Et (2-methyl-4- thiazolylmethyl)phosphonate in THF-hexane containing Buli to give (E,3S)-1-[[dimethyl(1,1-dimethyl)silyl)sxy]-3-([(1,1-dimethylethyl)silyl)]oxy]-4-(2-methylthiazol-4- ene.

New method for the preparation of the C(1)-C(6) -segment of epothilons and epothilone . Klar, Ulrich; Schwede, Wolfgung; Skuballe, Werner; Buchmann, Rernd; CAPLUS COPYRIGHT 2007 ACS on STN 1999:116657 CAPLUS Full-text Schering A.-G., Germany Ger. Offen., 12 pp. CODEN: GWXXBX Schirner, Michael derivatives 130:168162 Patent German FAMILY ACC. NUM. COUNT: PATENT INFORMATION: L102 ANSWER 24 OF 24 ACCESSION NUMBER: PATENT ASSIGNEE(S): SOURCE: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR (S): LANGUAGE

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# SN 10/563058 Page 25 of 172 STIC STN SEARCH RESULTS

DE 1998-19813821 WO 1998-EP5064

A 19980320 W 19980810

MARPAT 130:196529 OTHER SOURCE(S): GI

tetramethyloyclohexedec-13-en-2,6-dione (II) were prepared in many steps. The new compds. interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumors, such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, addenocarcinoma, malignant melanoma, and acute lyamphocytic and myslocytic leukemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, and invention can be used alone or, to achieve additive or synergistic effects, in combination with other principles and substance categories used in tumor etc.; Y = 0, H2; Z = 0, (H, OH), (H, protected OH); Rla, Rlb = H, alkyl, aryl, aralkyl, or together = (CH2)m where m = 2, 3, 4, 5; R2a, R2b = H, alkyl, aryl, aralkyl, or together = (CH2)m where m = 2, 3, 4, 5; when D-E = CH2CH2 or when Y = 0, R2a or R2b may not be H/Nds; R3 = H, alkyl, aryl, aralkyl; R4a, R4b = H, alkyl, aryl, aralkyl; R4a, R4b = H, alkyl, aryl, aralkyl; R5; D-E = CH2CH2, CH2H2, CTCH2, CT ,16S(E))-4,8-dihydroxydiseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, an for better tolerability of, medical implants, the derivs. can be introduced -(1-methy1-2-(2-methy1-4-thiazoly1)etheny1)-1-oxa-5,5,9,13-The compds. provided 7R,8S,9S,13E,16S(E))- and (4S,7R,8S,9S,13Z into or applied to polymeric materials. '- ethyl-16therapy. 2

CAPLUS COPYRIGHT 2007 ACS on STN 1999:116659 CAPLUS Full-text 130:168164 LIO2 ANSWER 22 OF 24 C ACCESSION NUMBER: DOCUMENT NUMBER: TITLE:

New (C1-C6)-fragments, method for their preparation and their application for synthesis of epothilone and

Klar, Ulrich; Schwede, Wolfgang; epothilone derivatives

INVENTOR(S):

Skuballa, Werner; Buchmann, Bernd;

Schirner, Michael Schering A.-G., Germany Ger. Offen., 18 pp.

PATENT ASSIGNEE(S): SOURCE:

# SN 10/563058 Page 26 of 172 STIC STN SEARCH RESULTS

CODEN: GWXXBX Patent German DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

PA	PATENT NO.			KIND		DATE			\PPL	APPLICATIO	APPLICATION NO	9		ם ו	DATE	
1 12	19735578			l A		19990211	0211	' "	DE 1	-766	1997-19735578	5578	 	7	19970809	608
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$$^{\text{R3}}_{\text{CZ}}$$
  $^{\text{R6}}_{\text{OR}}$   $^{\text{OR}}_{\text{OR}}$ 

III

The title compds. [I; II; III; R1, R2 = H, alkyl, aryl, aralkyl; R3 = CH2OH, CH2OR; R4 = OH, OR; R = CR7R8; R7, R8 = H, alkyl, aryl, or R7R8 = (CH2)n; n = 2-6; R5, R6 = H, alkyl, aralkyl, or R5R6 = (CH2)n; m = 2-5; R9, R10 = H, CH2OR; R4 = OH, OR; R = CR7R8; R7, R8 = H 2-6; R5, R6 = H, alkyl, aralkyl, or R5R6 æ

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from which structure-activity- relationships can be deduced. Epothilone A (R=H) Epothilone B (R=Me) Epothilone C (R=H) Epothilone U (R=Me).

The preparation process, intermediate products and pharmaceutical use of epothilone derivatives Buchmann, Bernd; Klar, Ulrich; Skuballa, Warner; Schwede, Wolfgang; Michael; Menrad, Andreas APPLICATION NO. CAPLUS COPYRIGHT 2007 ACS on STN 2000:15195 CAPLUS Full-text Schering A.-G., Germany PCI Int. Appl., 86 pp. CODEN: PIXXD2 132:64110 Schirner, German Patent : TNDOO L102 ANSWER 20 OF 24 ACCESSION NUMBER: PATENT ASSIGNEE(S): SOURCE: FAMILY ACC. NUM. CO PATENT INFORMATION: DOCUMENT NUMBER: PATENT NO. DOCUMENT TYPE: INVENTOR(S): LANGUAGE: TITLE:

CN, CU, CZ, IN, IS, JP, MG, MK, MN, SL, TJ, TM, KG, KZ, MD, DE, DK, CF, CG, 19990513 9990630 19980630 19980630 19990513 £ 3 CA, CH, ID, IL, IV, MD, I SI, SK, 8 유, DE 1998-19830060 DE 1999-19923001 AU 1999-50369 DE 1998-19830060 DE 1999-19923001 AT, BE, PT, SE, 1 CASREACT 132:64110; MARPAT 132:64110 1999-EP4915 Š, Š ΣW SE, ZW, Z, SD, ZA, NG, sz, m, ¥ S É E B SL, 20000106 82, 1C, 1C, 1Z, SD, IE, ¥ £ € PL, US, 3 8 . 388 ģ Ä 2 Z 4 SERT S PRIORITY APPLN. INFO.: KG, EE, 55.85.9 WO 2000000485 DE 19830060 DE 19923001 AU 9950369 Æ, ES. OTHER SOURCE(S): GI Ж Ж

# \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

C1-10-hydroxyalkyl, C1-10-haloalkyl; X = 0, (0R9)2, C2-10-alkylene-q, \tilde{\omega} - \text{dioxy}, CR11R12; CX = CH(0R10); R9 = C1-20-alkyl; R10 = H, protecting group; R11, R12 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R11R12 = CH2, C5-7-carbocyclic ring; Y = 0, CY = CH2; CZ = CH(0R13), R13 = H, protecting group] which are prepared via cyclization of ketones II [R15 = H, 0H halogen, OR15t, OS02R15b; R15a = H, S02-alkyl, S02-aryl, S02-aralkyl, (CH2)0, CR16eR16b; R15b = H, C1-20-alkyl, aryl, C7-20-aralkyl; aryl, C7-10-aralkyl; RlaRlb = (CH2)m, m = 2 - 5; R2a, R2b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R2aR2b = (CH2)n, n = 2 + 5; R3 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4a, R4b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4aR4b = C(H2)m, m = 2 - 5; D-E = CH2CH2, CH3CH, Cxtplond, C, oxirane ring, CH(OH2)m, CH(OH)CH(OH), CH(OH)CH2; R5 = C1-10-alkyl, aryl, C7-10-aralkyl; R6, R7 = H, R6R7 = 0, bond; R8 = C1-10-alkyl, aryl, C7-10-aralkyl; R25 = H, C1-10-alkyl, æ

# SN 10/563058 Page 24 of 172 STIC STN SEARCH RESULTS

R16aR16b = (CH2)q; o = 2 - 4; q = 3 - 6). Thus, epothilone derivative III was prepared via macrolactonization of carboxylic acid IV with 2,4,6-trichlorobenzoyl chloride and Et3N in THF followed by deprotection with aqueous CF3002H in CH2C12. I cooperate with tubulin by stabilizing formed microtubuli.

THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 1102 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

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REFERENCE COUNT:

# SN 10/563058 Page 21 of 172 STIC STN SEARCH RESULTS

for treating chronic inflammatory diseases (psoriasis, arthritis) and can be deposited on or in polymer materials in order to prevent uncontrolled cell proliferations on medical implants and to improve the compatibility. These derivs. can be used alone or in combination with other principles and classes of substances that can be used in the therapy of tumors to achieve additive or cell division phase-specifically and are suitable for treating malignant tumors such as cancers of the ovaries, stomach, colon, glands, breasts, lungs, head and neck, malignant melanoma and acute lymphocytic and myelocytic leukemia. These compds, are also suitable for anti-angiogenesis therapy and They are able to influence the stabilizing the microtubuli which are formed. synergistic effects.

Preparation of epothilone derivatives useful as Buchmann, Bernd; Schwede, Wolfgang; Schirner, Michael pharmaceuticals Klar, Ulrich; Skuballa, Werner; 2000:573798 CAPLUS Full-text Schering A.-G., Germany PCT Int. Appl., 141 pp. CODEN: PIXXD2 133:177064 Patent German CAPLUS SOUNT: L102 ANSWER 18 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: PATENT ASSIGNEE(S): LANGJAGE:
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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

prepared Thus II was prepared in a multistep sequence from the starting materials III and IV. The novel compds. interact with tubulin by stabilizing the formed microtubuli. The compds. are able to influence the cell division in RID = Me; R2 = Me, Et, Pr; X = 2-pyridyi, 2-methyl-4-thiazolyl or 2-methyl-4-owazoly; and the N and/or S atoms in X can be in a oxidized form; and if R2 and R8 = Me; X can only be a 2-pyridyl residue which is optionally oxidized at the nitrogen atom) and all possible stereoisomers and their mixts were conjunction with addnl. constituents and substance classes which can be use in example, ovarian cancer, gastric carcinoma, colon cancer, breast cancer, lung cancer, head and neck cancer, malignant melanoma, and acute lymphocytic and myelocytic leukemia. The inventive compds. are suited for use in antimorphogenic therapy as well as for treating chronic inflammatory diseases (psoriesis, arthritis). In order to prevent uncontrolled cell proliferations and to improve the compatibility of medical implants, the inventive compds. can be applied or incorporated in polymeric materials. The inventive compds. can be used alone or, in order to achieve additive or synergistic effects, in Novel epothilone derivs. I (R4 = R5 = H, C1-C10 alkyl, aryl, C7-C20 aralkyl; R6, R7 are each H, or together an addnl. bond or O; R8 = Me or H; R1a, R1b together = trimethylene; R2 = Ph, CH2Ph; X = 2-pyridyl, 2-methyl-d-thiacolyl, 2-methyl-d-oxacolyl, or R1a, R1b together = trimethylene; R2 = Me, Et, Pr; X 2-pyridyl, 2-methyl-d-thiacolyl, 2-methyl-2-methyl-d-thiacolyl, 2-methyl-resould R1a = 2-pyridyl, 2-methyl-d-thiacolyl, 2-methyl-d-oxacolyl; or simultaneously R1a = phase-specific manner and are suited for treating malignant tumors, for æ

Berlin, D-13342, Germany
Book of Abstracts, 219th ACS National Meeting, San
Francisco, CA, March 26-30, 2000 (2000), ORGN-288.
American Chemical Society: Washington, D. C. Preclinical Drug Research, Schering AG, Germany, Klar, Ulrich; Skuballa, Kerner; Schwede, Wolfgang; Buchmann, Bernd COPYRIGHT 2007 ACS on STN: 332415 CAPLUS Full-text Conference; Meeting Abstract 2000:332415 CAPLUS CODEN: 69CLAC Epothilones CAPLUS L102 ANSWER 19 OF 24 ACCESSION NUMBER: CORPORATE SOURCE: DOCUMENT TYPE: AUTHOR(S): SOURCE:

The new natural product class of epothilones seems to parallel the biol English LANGUAGE: AB The

behavior of paclitaxel regarding its action on the tubulin system although the chemical structures are quite different. Despite its impressive antiproliferative effects also against multi drug resistant cell lines epothilone shows severe toxicity at therapeutic relevant doses in vivo. Thus the need which allows an efficient preparation of large ants. of strategic important building blocks with high optical purity, high flexibility regarding structural modifications in most parts of the mol., efficient syntheses of nethodol., more than 250 analogs of epothilone B and D have been synthesized for epothilone analogs with improved properties is obvious. In contrast to paclitaxel structural modifications can be achieved more easily by total synthesis. Therefore we have developed a highly convergent total synthesis analogs yielding sufficient amts. for in vivo characterization. Using this

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Epothilone derivs. I (RIa, RIb = H, Cl-Cl0-alkyl, aryl, C7-C20-aralkyl; (CH2) m = 1-5; CH20GH2; R2a, R2b = H, Cl-Cl0-alkyl, aryl, G7-C20-aralkyl; (GH2) n = acyl, C1-C20-acyloxy, OR24, O22R4, N3, N02, NR24aR24b; R4a, R24 = R24, C1-C20-acyloxy, OR24, O22R4, N3, N02, NR24aR24b; R4a, R24 = R24, C1-C20-acyloxy, OR24, N3, N02, NR24aR24b; R4a, R24 = R24, C1-C20-acyloxy, OR24, N3, N02, NR24aR24b; R4a, R24 = R24, C1-C30-alkyl, R5 = H, C1-C10-alkyl, aryl, C7-C20-aralkyl, R14 = H, OR14a, halogen; R3 = N C1-C10-alkyl, aryl, C7-C20-aralkyl, R14 = H, Dond, O; R8 = H, F C1-C10-alkyl, R2 = H, Protecting group; R6,R7 = H, bond, O; R8 = H, F C1-C10-alkyl, aryl, C7-C20-aralkyl, R6,R7 = H, bond, O; R8 = H, F C1-C10-alkyl, R9 = H, Protecting group; R6,R7 = H, bond, O; R8 = H, F C1-C10-alkyl, aryl, C7-C20-aralkyl, C7

Preparation of new epothilone derivatives and their Skuballa, Werner; Buchmann, Bernd; Michael; Menrad, Andreas Klar, Ulrich; Schwede, Wolfgang; CAPLUS COPYRIGHT 2007 ACS on STN 2000:592719 CAPLUS Full-text Schering A.-G., Germany PCT Int. Appl., 54 pp. pharmaceutical CODEN: PIXXD2 133:193025 Schirner, L102 ANSWER 17 OF 24 PATENT ASSIGNEE(S): ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR(S): SOURCE:

SN 10/563058 Page 20 of 172 STIC STN SEARCH RESULTS

LANGUAGE: German FAMILY ACC, NUM. COUNT: 1 PATENT INFORMATION:

8 % B % 8 当古 19990218 20000218 19990218 SI, ОН, СҮ, ВF, ВЈ, ï, ž À K BE, SZ, TZ, UG, ZW, AT, B , IT, LU, MC, NL, PT, S , MR, NE, SN, TD, TG DE 1999-19908760 DE 1999-19908760 sp, APPLICATION NO. WO 2000-EP1331 \$ \$ \$ \$ \$ 383 # F PT, US, P.F. 8 G MARPAT 133:193025 2000082 SL'AB'Z 12 Z A2 A3 Š KE, FI, PRIORITY APPLN. INFO.: OTHER SOURCE(S): WO 2000049019 WO 2000049019 IS, MG, SL, BY, GH, DE 19908760 Ä PATENT NO. RW:

Epothilone derivs. I (Rla, Rlb = H, Cl-Cl0 alkyl, aryl; C7-C20 aralkyl; or together are (CR21m m = 1-5; or CH2CH2; Rza, RD2 = H, C1-C10 alkyl, aryl; C7-C20 aralkyl; or together are (CH2)n n = 2-5; 01-G-E-E1 = CR3aR3b-CR4-CH2L2 CR3aR3b-CR(H)R4-CR2 (RR3a-RR4-CH2) CR3aR3b-CR4-CH2 CR3aR3b-CR4-CH2 (RR3a-RR4-CH2) CR3aR3b-CR4-CH2 CR3aR3b-CR4-CH2 CR3aR3b-CR4-CH2 CR3aR3b-CR4-CH2 CR3aR3b-CR4-CH2 CR3a-CR4-CH2-CH where RSa = H, C1-C10 alkyl; C7-C20 aralkyl; R14 = H, OR14a, halogen, OSCS14b; R3 = H, C1-C10 alkyl, aryl; C7-C20 aralkyl; R14 = H, OR14a, halogen, OSCS14b; R3 = H, C1-C10 alkyl, aryl; C7-C20 aralkyl; R5, R7 = H, O, bond; R8 = H, C1-C10 alkyl, aryl; C7-C20 aralkyl; X = O, OR23, C2-C10-alkylene-a,a- dihydroxy which can be a straight chain or branched; H/OR9 or the group CR10R11 where R23 = C1-C20 aralkyl; R9 = H or a protecting group; R10,R11 = H, C1-C20 alkyl, aryl; C7-C20 aralkyl or R10,R11 together form a 5-7 membered carbocyclic ring; Y = O or Z H atoms; Z = O or H/OR12 where R12 = H or a protecting group) were prepared in addition to all possible stereoisomers and mixts. Thus II was prepared from (1)-1-acctoxypantan-4 one in a multiticep synthesis. Those epothhlone derivs, interact with tubulin by

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SN 10/563058 Page 18 of 172 STIC STN SEARCH RESULTS

16-Halogen epothilone derivs. I (Rla, Rlb = RZa, RZb = H, Cl-ClO-alkyl, aryl, C7-C20-aralkyl, (CH2)m = 2-5; R3 = H, Cl-ClO-alkyl, aryl, C7-C20-aralkyl, (CH2) Ra, Rdb = H, Cl-ClO-alkyl, aryl, C7-C20-aralkyl, (CH2)p p = 2-5; D-E = 1, Z-ethanediyl, 1,Z-ethanediyl, chypyl, oryl-caralkyl, (CH2)p p = 2-5; D-ethanediyl, 1(2)-hydroxy-1,Z-ethanediyl, CH2OH; R5 = H, Cl-ClO-alkyl, aryl, C7-C20-aralkyl, DC2H, C02-alkyl, CH2OH; R5 = H, Cl-ClO-alkyl, aryl, C7-C20-aralkyl, aryl, C7-C20-aralkyl, CA2-Alkyl, CH2OH; R6, R7 = H, bond, O; R8 = halogen, CN; X = O, two alkoxy groups OR22, C2-ClO-alkylane-a, 0-dlipydroxy group straight or branched chain, H/OR9, CH1OR11 where R23 = Cl-C20-alkyl; R9 = H, or protecting group; R10, R11 = H, Cl-ClO-alkyl, aryl, C7-C20-aralkyl, 5-7 membered carbocyclic ring; T-Y = OC(-0), OCI2, CH2C(-0), NR24C(-0), NR24SO2; R24 = H, Cl-ClO-alkyl, Z = O, H/OR12 where R12 = H or protecting group) were prepared in addition to all possible stereoisomers and mixts. Thus II was prepared II was 5.1 mM on MCF-7 breast tumor and had an IC50 of 37 mM on the multidrug resistant carchoma NCI/ADR.

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L102 ANSWER 16 OF 24	L102 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN ,
ACCESSION NUMBER:	2000:592720 CAPLUS Full-text
DOCUMENT NUMBER:	133:193027
TITLE:	Preparation of new epothilone derivatives having
	pharmaceutical application as antitumor agents
INVENTOR(S):	Klar, Ulrich; Schwede, Wolfgang;
	Buchmann, Bernd; Skuballa, Werner;
	Schirner, Michael; Grimm, Michael
PATENT ASSIGNEE (S):	Schering Aktiengesellschaft, Germany
SOURCE:	PCT Int. Appl., 70 pp.

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•	scultuer, Michael;
PATENT ASSIGNEE (S):	Schering Aktiengese
SOURCE:	PCT Int. Appl., 70
	CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	-
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000049020 WO 2000049020	A2 A3	20000824 20001228	WO 2000-EP1332	20000218

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# SN 10/563058 Page 15 of 172 STIC STN SEARCH RESULTS

20011019	20011026	20011029	20011030	20011129	20020606	20041018	20050802.	20050831	20070411	19990430	19991104	20000309	200003	20000501	20000501	20011019	20020606	
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2001-MN1305	"	1.0	2001-PA11039		.,	••	2005-MN837	2005-214988	2007-104224	1999-19921086	1999-19954228	2000-10013363	2000-10015836	2000-615619	2000-IB657	2001-MN1305	2002-979939	
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IN 2001MN01305	BG 106053	NO 2001005278		ZA 2001009859	US 7125893	US 2005113429	IN 2005MN00837	US 2006046997	JP 2007224038	PRIORITY APPLN. INFO.:						•		
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up the mols. Thus, [45,7R,85,95,132,165(E)]-4,8-dihydroxy-16-[1-methyl-2-(2-pyi4dy) ethemyly]-1-oxclohexadecene-2.5-dione was prepared in several steps starting from (45)-4-(2-methyl-1-oxclohexadecene-2-propyl)-2,2-dimethyl[1,3]dioxane and 5-(trimethylsily)-4-pentynylmagnesium The title compds. were prepared by various combinations of 3 fragments making MARPAT 133:321769 OTHER SOURCE(S): AB The title c

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Preparation of new epothilone derivatives and their 19990218 DE 1999-19908767 DE 1999-19908767 Skuballa, Werner; Buchmann, Bernd; APPLICATION NO. Klar, Ulrich; Schwede, Wolfgang; 2000:738730 . CAPLUS Full-text COPYRIGHT 2007 ACS on STN Schering A.-G., Germany Ger. Offen., 74 pp. CODEN: GWXXBX Michael MARPAT 133:309795 20001019 pharmaceutical KIND DATE 133:309795 Schirner, Patent German A1 CAPLUS OOUNT: DE 19908767 PRIORITY APPIN. INFO.: OTHER SOURCE(S): LIO2 ANSWER 14 OF 24 ACCESSION NUMBER: PATENT ASSIGNEE (S): FAMILY ACC. NUM. CO PATENT INFORMATION: DOCUMENT NUMBER: PATENT NO. DOCUMENT TYPE: INVENTOR(S): LANGUAGE: SOURCE: LITLE: ß

SN 10/563058 Page 16 of 172 STIC STN SEARCH RESULTS

H

alkylene-a, a-dloxy group straight or branched, OR9 or the CRIORII group where R23 = alkyl, R8 = H or protecting group and R10,R11 = same or different H, alkyl, aryl, aralkyl or R10,R11 = together with methylene are a 5-7 membered carbocyclic ring; Y = 0 or two H; Z = 0 or H/OR12 and R12 = H or a protecting group) were prepared Thus E- and Z-II were prepared via a multistep synthesis. I cooperate with tubulin by stabilizing formed microtubuli. I are able phase specifically to affect the cell division and are suitable for the treatment of malignant ovarian, stomach, colon, acieno, breast, lung, head and can be used alone or to achieve additive or synergistic effects in combination with further principles and substance classes applicable in tumor therapy. eryl, aralkyl or (GH2)m,n m, n = 2-5; R3 = H, alkyl, aryl, aralkyl; R4a,R4b = same or different H, alkyl, aryl, aralkyl or (GH2) = 2-5; GH2GH2, CH-GH, CC-tplbond.C, epoxy, GH(GH3)(H(H), GH(GH3)(H2; D-E = a group; R5 = H, alkyl, aryl, aralkyl; R6,R7 = H, bond, 0; R8 = H, alkyl, aryl, aralkyl; X = 0, OR23 uncontrolled cell proliferations and to improve the compatibility of neck tumors, malignant melanomas, acute lymphocytic and myelocytic leukemia. medical implants I can be applied or incorporated into polymeric materials. I are suitable for use in anti-angiogenic therapy as well as for ronic inflammatory diseases (psoriasis, arthritis). In order to New epothilone derivs. I (Rla, Rlb = R2a, R2b = same or different H, alkyl, treating chronic Derivs. of prevent

Preparation of 16-halogen epothilone derivatives and Schering Aktiengesellschaft, Germany PCT Int. Appl., 105 pp. Buchmann, Bernd; Schwede, Wolfgang; 1US COPYRIGHT 2007 ACS on STN 2000:592721 CAPIUS Full-text their use as antitumor agents . Klar, Ulrich: Skuballa, Warner; Schirner, Michael 133:193028 PATENT ASSIGNEE(S): ACCESSION NUMBER: DOCUMENT NUMBER: INVENTOR(S): SOURCE: TITE:

CAPLUS

L102 ANSWER 15 OF 24

CODEN: PIXXD2 German Patent COUNT FAMILY ACC. NUM. OC PATENT INFORMATION: DOCUMENT TYPE:

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# SN 10/563058 Page 13 of 172 STIC STIN SEARCH RESULTS

FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

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APPLICATION NO.	WO 2000-IB657 BB, BG, BR,	FI, GB, GD, GE, KR, KZ, LC, LK,	NZ, PL,	UA, UG,	UG, ZW,	LU, MC, NL,	ž į		DE 1999-19954228			BR 2000-10190	EP 2000-922826	GR, IT, LI, LU,		JP 2000-615619	EE 2001-568	NZ 2000-514989	AU 2000-43103	IN 2001-MN1305	BG 2001-106053	NO 2001-5278				US 2005-214988	DE 1999-19921086	DE 1999-19954228	DE 2000-10015836	DE 2000-10013363	WO 2000-IB657	IN 2001-MN1305	US 2002-979939		
	109 AZ,	KG, KP,	MW,	TR,	SL,	IE,	ME, MR,	20001102	20010913	11011	20001109	20020108	20020123	ES, FR, GB,		20021217	20030217	20040227	20040506	20070504	20020531	20011221	20030630	20061024	. 80902002	20060302								362656	
DATE	AT,	DM, DZ, JP, KE,	MK, MN,				% € €	2000	200	200	2000	2003	2002	DK, ES,	8	2002	. 200	200	* 200	. 200.	÷ 200	\$ 200]	. 200	2006	200	2006		•-						MARPAT 133:362656	
KIND		DK,		-			G	Y.	¥ :	7	¥.	4	A1	DE,	FI,	H	K	K	B2	K	K	×	¥.	B1	K	Al	•	-	,i					MARE	
!	-	CZ, DE, IL, IN,	_				Ę.							£,	N I								_		_		 o								•
PATENT NO.	0006658 : AE,	Q, CZ, ID, IL,		SG, SI,									P 1173441	R: AT, BE,	SI, LT,	2002	E 200100568		J 772750	IN 2001MN01305	G 106053	2001005278		s 7125893	N 2005/MN00837	US 2006046997	PRIORITY APPLIN. INFO							OTHER SOURCE(S):	
aŭ i	) Ž						i	ďΪ	30 E	ij	ð	BR	EP			A.	33	NZ	DA.	=	BG	S S	ž	SN	Zi	Š	PRIORI:							OTHER :	ម

# \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

The antitumor agents, 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilones I (Rla, Rlb are same or different = H, Cl-Cl0 alkyl, C6-Cl2 aryl, C7-C20 aralkyl each optionally substituted; or together = (CH2)m = 1-5 or '-CH2OR12', R26(R2b replace a with b) = H, substituted alkyl, aryl, aralkyl, (CH2) ra-C. tpibond. (or =)C-(CH2)pa-R26a, Q, Ql where n = 0-5; ra, rb = the same or different and = 0-4; pa, pb = the same or different and = 0-3; R3 = H, substituted alkyl, aryl or aralkyl, R3b = 0H, OPG14; R14 = H, OR14a, Andogen and R14a = H, S02-alkyl, S02-aryl or S02-aralkyl; R4 = H, substituted alkyl, aryl or aralkyl, halogen, R25, CN; R26a, R26b = same or different = H, substituted alkyl, aryl or aralkyl, c1-Cl0 acyl or if pa or pb > 0, addnl. a group OR27; R25 = R27 = R22 aralkyl, C1-Cl0 acyl or if pa or pb > 0, addnl. a group OR27; R25 = R27 = R22 or halogen; R6, R7 = H or together = bond or 0; G = X=CR8 or bi- or tricyclic æ

# SN 10/563058 Page 14 of 172 STIC STN SEARCH RESULTS

= 0, two OR23 groups, C2-C10-alkyjene-a, dedioxy straight chain or branched;
H/OR9 or CR10R11 group and R23 = alkyl radical, R9 = H, PG, R10, R11 = same or
different = H, substituted alkyl, aryl or aralkyl, or together with the
methylene are a 5-7 carbodyclic tring; D-E = CR2CH2 or CCH2; A = OC(0), OCH2,
CH2C(0), NR29C(0), NR29SO2 and R29 = H, alkyl; Z = 0 or H/OR12 and R12 = H,
PG) were prepared thus II was prepared in a multistep synthesis starting from
(4S)-4-(2-methyl-1-oxoprop-2-yl)-2-dimethyll; Jdioxane and 5trimethylsilylpent-4-in-1-yl magnesium bromide. Il had an IC50 value [nM] of
3.0 for the growth inhibition of human MCF-7 breast- and 75 for multidrug
resistant NCI/ADR carchonae cell ilnes with a selectivity of 2.5. The new
epothilone derivs, interact with tubulin by stabilizing microtubuli that are
formed. They are able to influence the cell-splitting in a phase-specific
manner and are therefore useful in treating diseases or conditions associated
with the need for cell growth, division and/or proliferation. Thus the
spoothilone derive, are suitable for treating malignant tumors, e.g., ovarian,
stomach, colon, adeno-, breast, lung, head and neck carcinomas, malignant
melanoma, acute lymphocytic alwayers, end of pressing the content of the content aryl radical and R8 = H, halogen, CN, or substituted alkyl, aryl or aralkyl; X therapy as well as for treatment of chronic inflammatory diseases (such as psoriasis, arthitis).

REFERENCE COUNT:

4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THEE

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 6-Alkanyl and 6-alkynyl derivatives of epothilone Klar, Ulrich; Schwede, Wolfgang; Skuballa, Warner; Buchmann, Bernd; Hoffmann, Jens; Lichtner, Rosemarie Schering A.-G., Germany Ger. Offen., 18 pp. ODEN: GWXXBX 2000:772379 CAPLUS Full-text 133:321769 Patent CAPLUS LIO2 ANSWER 13 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: PATENT ASSIGNEE(S): SOURCE: INVENTOR(S):

German 3 FAMILY ACC. NUM. COUNT: PATENT INFORMATION: DOCUMENT TYPE: LANGUAGE:

11 20001102 DE 1999-199210B6 11 20001109 CA 2000-2371226 11 20001109 WO 2000-18657, 1, AT, AU, AZ, BA, BB, BG, BR, BY, CA, 1, DM, DZ, EE, ES, FI, CB, CD, GE, CH, 1, AT, AU, AZ, AZ, AZ, AZ, CA, CA, CA, CA, CA, CA, CA, CA, CA, CA
CA 2000-23712; WO 2000-1B657 A, BB, BG, BR, E S, FI, GB, GD, G P, KR, KZ, LC, I
WO 2000-IB657, A, BB, BG, BR, BY S, FI, GB, GD, GE P, KR, KZ, LC, LK
A, BB, BG, BF S, FI, GB, GI P, KR, KZ, LC X NO N7 P
S, FI, GB, P, KR, KZ, NO N7
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# SN 10/563058 Page 11 of 172 STIC STN SEARCH RESULTS

Subcellular distribution of epothilones in human tumor Lichtner, R. B.; Rotgeri, A.; Bunte, T.;

B.; Hoffmann, J.; Schwede, W.; Skuballa, W.; Klar,

CORPORATE SOURCE:

SOURCE:

AUTHOR(S):

Research Laboratories of Schering AG, Berlin, 13342, Germany

Proceedings of the National Academy of Sciences of the United States of America (2001), 98(20), 11743-11748 CODEN: PMASA6; ISSN: 0027-8424 National Academy of Sciences

Journal

English DOCUMENT TYPE:

analogs, 6-propyl-bpoB (pEB) and 6-propyl-bpoD (pED), in comparison with the natural compds. EpoB/EpoD, by using human A431, MCF7, and MDR1-overexpressing NCI/Adr cells. By using tritiated pEB/pED, compound uptake, release, and nuclear accumulation were investigated in A431 and NCI/Adr cells. In these cells, epothilones can principally be recognized and exported by verapamil-sensitive efflux pumps, which are not identical to MDR1. The degree of export nM, resp., was increased in the presence of 10  $\mu\text{M}$  Verapamil in both cell lines 2- to 8-fold. In contrast, the intracellular levels of pEB were affected by Verapamil only at 3.5 nM pEB in NCl/Adr (2-fold) and not in A431 cells. In Epothilones are a new class of natural and potent antineoplastic agents that stabilize microtubules. Although 12,13-epoxide derivs. are potent antiproliferative agents, the activities of the corresponding 12,13-olefin analogs are significantly decreased. These data were confirmed for two new depends on the structure, olefin vs. epoxide-analog, and also on the intracellular drug concentration. The accumulation of pED used at 3.5 or  $70\,$ LANGUAGE:

pacifitaxel or pED (5-15%) in both cell lines. Our study suggests that differences in growth inhibitory efficacy between epoxide and olefin analogs may be based on different mechanisms of drug accumulation and subcellular THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 34

addition, strong nuclear accumulation was observed for pEB (40-50%) but not

2001:676638 CAPLUS Full-text CAPLUS L102 ANSWER 11 OF 24 ACCESSION NUMBER:

DOCUMENT NUMBER:

135:236394 Synthesis of radioactively labeled epothilone derivatives and their biochemical and pharmaceutical Klar, Ulrich; Gay, Juergen; Skuballa,

Buchmann, Bernd; Bunte, Thomas; Lichtner, Wolfgang; Werner; Schwede, Rosemarie

Schering Aktlengesellschaft, Germany PCT Int. Appl., 31 pp. CODEN: PIXXD2 Patent

PATENT ASSIGNEE(S):

SOURCE:

INVENTOR(S):

German FAMILY ACC. NUM. COUNT: PATENT INFORMATION: DOCUMENT TYPE: LANGUAGE:

20010309 유. 보. 보. 구. ક્ કુ ગ્ર £,4,8 BG, BR, BY, GB, GD, GE, KZ, LC, LK, APPLICATION NO. WO 2001-EP2699 BB, FI, KR, ¥ 8 & 対照改 20010913 AC, CZ, KE, なる。 KIND AZ AM, DK, IS, AE, AG, AL, P CR, CU, CZ, I ID, IL, IN, 1 WO 2001066154 PATENT NO.

# SN 10/563058 Page 12 of 172 STIC STN SEARCH RESULTS

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and represent, independent of one another, hydrogen C1-C10 alkyl, aryl, C7-C20 aralkyl or, together, represent a (GH2)m group, where m is equal to 1, 2, 3, 4 or 5; X say represents a C2-C10 alkyl group, a C2-C10 alkyl group, a C2-C10 alkyl group, a C2-C10 alkyl group, a C2-C10 alkyl group or a C3-C20 aralkyl each containing 2n tritum atoms, where n equals 1 or 2; R4 represents 0-PG and hydroxyl; R5 represents hydrogen C1-C10 alkyl, aryl, C7-C20 aralkyl and halogen; W2 represents a C42-C42, C41-C or O-C42 group; R6 represents hydrogen, C1-C10 alkyl, aryl, C7-C20 aralkyl, (GH2)s-V and halogen, where 3 equals 1, 2, 3 or 4 and V represents O-PG, hydroxyl or halogen; R7, R8 each represents an O-C(=O), an O-CH2, a CH2-C(=O), an NR11-C(=O) and an NR11-SO2 group, wherein R11 represents hydrogen and C1-C10 alkyl. The novol compas, of formula I are valuable pharmacend and valuable diagnostic probes for alucidating, for example, active mechanisms and biocham, pharmacekinetic epothilone derivs. of general formula (1), where Ri represents O-PG and hydroxyl, where PG is a protective group; R2a, R2b are the same or different The invention relates to novel radioactively labeled pharmacol. effective and/or pharmacodynamic processes. 2

Preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothlione derivatives and their antitumor activity CAPLUS COPYRIGHT 2007 ACS on STN 2000:790507 CAPLUS Full-text 133:362656 L102 ANSWER 12 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER:

Skuballa, Werner; Buchmann, Bernd; Klar, Ulrich; Schwede, Wolfgang; Jens; Lichtner, Hoffmann,

INVENTOR (S):

Schering Aktiengesellschaft, Germany PCT Int. Appl., 298 pp. CODEN: PIXXD2 PATENT ASSIGNEE(S): DOCUMENT TYPE: LANGUAGE: SOURCE:

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Oxa-epothilones, such as I [R3 = heteroaryl, heteroarylalkenyl, heteroarylhaloalkenyl, terestrylhaloalkenyl, alkyl, arylalkyl; R8R8a = alkylens, heteroarylhaloalkenyl, alkyl, arylalkyl; R8R8a = alkylens, heteroalkens; R10 = H, alkyl, alkynyl; R1R16a = bond, O; R16 = H, CN, alkyl, halogen; X = O, NHJ, were prepared for a variety of therapeutic uses, such as treatment of malignant tumors, proliferative diseases, leukemia, and chronic inflammatory diseases, as well as for anti-anglogenic SE therapy. Thus, oxa-epothilone II was prepared via a multistep syminetic sequence starting from (R)-1,2-propanediol, and [135,42)-3-[[(1,j]-dimethylethyl)dimethylsilyl)oxyl-4-fluoro-5-(2-methyl-4-thiazolyl)-4-pentenyl briphenylphosphonium iodide,. Pharmaceutical formulations of the prepared oxa-epothilones were discussed, but specific biol. activity data was not presented.

L102 ANSWER 9 OF 24 CAPLUS COPPRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:780370 CAPLUS Full-text
DOCUMENT NUMBER: 135:33129 CAPLUS Full-text
DOCUMENT NUMBER: 135:33129 CAPLUS Full-text
TITLE: Preparation of epothilone derivatives for pharmaceutical use in the treatment of cancer pharmaceutical use in the treatment of cancer INVENTOR(S): Brobmann, Barnal Rar, Unitabl; Schwede, Folgang; Hoffmann, Jens; Lichtner, Rosemarie Schering A.-G., Germanny SOUNCE: Ger: Offen., 42 pp.
DOCUMENT TYPE: German Patent
LANGUAGE: German German
FAMILY ACC: NUM: COUNT: 1
PATENT NOC: NUM: COUNT: 1

DATE		20000419	20010419
APPLICATION NO.		DE 2000-10020517	WO 2001-EP4552
DATE		20011025	20011101
KIND	1	A1	A2
PATENT NO.		DE 10020517	WO 2001081342

### SN 10/563058 Page 10 of 172 STIC STN SEARCH RESULTS

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OTHER SC GI	SOURCE (S)	(8)			MARPAT	AT 1	35:3	135:331294	4									

AB Epothilones, such as I [R3 = heteroaryl, heteroarylalkenyl, R8RBa = alkylene, heteroarylhaloalkenyl,etc.; R8, R8a = H, alkyl, arylalkyl; R8RBa = alkylene, heteroalkene; R10 = H, alkyl, alkenyl, alkynyl; R1R16a = bond, 0; R16 = H, CN, alkyl, halogan; X = O, NH; X1 = O, CH2], were prepared for a variety of therapeutic uses, such as treatment of malignant timors, proliferative diseases, leukemia, and chronic inflammatory diseases. Thus, epothilone II was prepared via a multistep synthetic sequence starting from (3S)-dihydro-3-hydroxy-4,4-dimethyl-2(3H)-furanone, L-(-)-malic acid, and [(2-methyl-4-thiazolyl)methyl]phosphonic acid di-Et ester. Pharmacoutical formulations of the prepared owa-epothilones were discussed, but specific biol. activity data was not presented.

L102 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2001:729040 CAPLUS Full-text DOCUMENT NUMBER: 136:95676

### SN 10/563058 Page 7 of 172 STIC STN SEARCH RESULTS

CA, CH, CN, GE, GH, GM, LK, LR, LS, OM, PH, PL, TT, TZ, UA, AM, AZ, BY, DK, EE, ES, TR, BF, BJ, TG 20021223 20021223 20011221 20021223 20021223 20011221 ZW, DE, SK, DE 2001-10164592 AU 2002-356783 US 2002-326263 DE 2001-10164592 WO 2002-EP14758 CASREACT 139:85166; MARPAT 139:85166 SI, SZ, X Š.Š SZ, TZ, UG, BG, CH, CY, NL, PT, SE, ML, MR, NE, វ ខ ፠፠፠፠*ጜ*፠፠፠ AT, ₹ <sub>P</sub> કું કુ PRIORITY APPLN. INFO.: DE 10164592 AU 2002356783 US 2003176710 OTHER SOURCE(S): Ĕ RW: ij

RISYR157

AB The invention relates to C1-C6 fragments I [R1a, R1b = H; C1-10-a1kyl, aryl, C7-20-aralkyl, (GH2)m m = 2 - 5; R2a, R2b = H, C1-10-a1kyl, C1-10-a1kyl, C1-10-a1kyl, C1-10-a1kyl, C1-10-a1kyl, C1-10-a1kyl, C1-20-aralkyl, (GH2)m m = 2 - 5; R1a, R15b = H, C1-10-a1kyl, C1-20-aralkyl, (GH2)g; q = 3 - 6] of epothilones and to an efficient method for producing such fragments and the darivs.-theroof. Thus, (45)-q-(2-methyl-3-oxohept-6-an-2-yl)-2,2-dimethyl-13-dioxane [1; R1a = R1b = Me, R2a = GH2CH:GH2, R2b = H, R15a = R1b = Me) was prepared from (35)-1-hydroxy-2,2-dimethyl-3-(tetrahydropyranyloxy)-4- pentene, (5)-HOCH2CMe2CH(OTHP)CH:CH2, via 0-benzylation with PGGH2Er, hydroboration with Mey2COMe) 2 in MeCOMe containing catalytic tosyl acid, hydrogenolytic debenzylation, Snern oxidation, Grigmard reaction with MeWgBr, oxidh, with TPAT in GH2C12 contg, NOmethylmorpholine N-oxide and alkylation with allyl bromide.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS REFORMAT

### SN 10/563058 Page 8 of 172 STIC STN SEARCH RESULTS

LIG2 ANSWER 7 OF 24 CAPLUS COPPRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:132142 CAPLUS Full-text
DOCUMENT NUMBER: 136:30977\*\*

TITLE:
AUTHOR(S): Research Leboratories of Schering AG, Berlin, D-13342, Burder, Thomas; Hoffmann, Jens; Lichtner, Rosemarie B. Research Leboratories of Schering AG, Berlin, D-13342, Germany
SOURCE: ACS PROPOSIUM Series (2001), 796(Anticancer Agents), 131-147
CODEN: ACSMCB; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal, General Review

PUBLISHER:
American Chemical Society
DOCUMENT TYPE:
Bugglish
AB A review. The total synthesis and biol, activity of epothilone analogs are described. Selected SAR data indicate the possibility to improve activity and selectivity by structural modifications. The new compds. may help to selectivity by structural modifications. The new compds. may help to allocidate the therapeutic potential of this class of anticancer drugs.

REFERENCE COUNT:
16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS REFERENCE COUNT:

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR RECORD. ALL CITATIONS AVAILABLE IN THE RE 1.102 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2001:780372 CAPLUS FUll-text DOCUMENT NUMBER: 155:331295 TITLE:

INVENTOR(S): Schwed: \*\*Palfgame; Tatz, Ulrich; Schwed: \*\*Palfgame; Barnd; Stuballa, Farnar; Buchmaun, Barnd; Hoffmann, Jens; Lichtner, Rosemarie Schering A.-G., Germany Ger. Offen., 46 pp. ODEN: GANXER:

SOUNCE:
CORP.,
CODEN: GAXXEN
DOCUMENT TYPE:
Patent
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

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THE REST OF THIS BIB INFORMATION WAS NOT AVAILABLE AT THE TIME OF PRINTING

# SN 10/563058 Page 5 of 172 STIC STN SEARCH RESULTS

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active ingredients II [AK = OC(:0), OCH2, CH2C(:0), NR29C(:0), NR29SO2; R29 = H, CI-6-alkyl] according to known methods. The invention also relates to the corresponding CI-CI2 fragments.

REFERENCE COUNT:

1 THERE ARE I CITED REFERENCES AVAILABLE FOR THIS
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THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT CAPLUS

Use of epothilones in the treatment of brain diseases associated with proliferative processes Lichtner, Rosemarie; Rotgeri, Andrea; Klar, Olztch, Hoffmann, Jens; Buchmann, Barnd; Schwede, Rolfgang; Skuballa, JUS COPYRIGHT 2007 ACS on STN 2003:719306 CAPLUS Full-text Schering A.-G., Germany PCT Int. Appl., 53 pp. CODEN: PIXXD2 139:240340 English 2 Werner Patent LANGUAGE:
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION: LIO2 ANSWER 4 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: PATENT ASSIGNEE(S): DOCUMENT TYPE: INVENTOR(S): SOURCE: TITLE:

RK, SL, TJ, TM, TN, TR, TT, TZ, UA, TM, ZW, ZW, AM, AZ, BY, BE, BS, CH, CY, CZ, DE, DK, EE, ES, U, MC, NL, PT, SE, SI, SK, TR, BF, SQ, GW, ML, MR, NE, SN, TD, TG EP 2002-4745

B, GR, IT, LI, LU, NL, SE, MC, PT, XY, AL, TR 20030228 20030228 SE, MC, PT, HU, SK 20030228 8 # E # 8 20030228 20030228 9. H. ୍ ଓ LI, LU, NL, BG, CZ, EE, CA 2003-2477403 AU 2003-215618 EP 2003-743360 BR 2003-8154
JP 2003-572570
MX 2004-PA8450
NO 2004-4175
EP 2002-4745
US 2002-361062P
WO 2003-EP2085 KP, KR, MX, MZ, TM, TN, APPLICATION NO. 2003-EP2085 A1 20030912 CA 2003-247 A1 20030916 AU 2003-215 A1 20041201 EP 2003-743 DE, DK, ES, FR, GB, GR, IT, LII, LU, FI, RO, MK, CY, AL, TR, BC છે 20050713 DK, ES, FR, FI, RO, MK, 20030912 20050825 ž š AI, DE, ID, IL, IV, WA, SD, VC, VN, VC, NW, IS, MW, ફેં 5,₹ KIND ÇZ,¥ 다. 당, 원 차, R: AT, BE, CH, IE, SI, LT, g BR 2003008154
JP 200552360
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NO 2004004175
PRIORITY APPLN. INFO.: **Š**. B មិដ GM, HR, P 15, LT, 11 15, LT, 11 16, LT, 11 17, LT, 11 18, CM, P 18, KZ, M R: AT, BE, ( IE, SI, 1 8, AG, R, GR, CA 2477403 AU 2003215618 EP 1480643 WO 2003074053 PATENT NO.

OTHER SOURCE(S): MARPAT 139:240340

AB The invention provides the use of an Epothilone, which shows an average distribution coefficient between plasma and brain of 0.1 to 1.5 in the mouse i.v. bolus injection assay for the preparation of a medicament for the treatment of a brain disease associated with proliferative processes.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

# SN 10/563058 Page 6 of 172 STIC STN SFARCH RESILL TS

SN 10/563058 Page 6 of 172		STIC STN SEARCH RESULTS	H RESULTS	
ACCESSION NUMBER:	2003:693140	93140 CAPLUS	US Full-text	
DOCUMENT NUMBER:	139:19	1465		
TITLE:	use or associ	Use or epothitones in associated with prolif	the trea erative	nt of brain diseases cesses
INVENTOR(S):	Lichtner, Bernd; Hof Schrede, I	er, Rosemarie; Hoffmann, Kari	Rotgeri, n; Kler,	Andrea; <b>Buchmann,</b> <b>Ulrich</b> ; brner
PATENT ASSIGNEE(S):	Scheri	Schering Aktiengesellschaft,		any
SOURCE:	Eur. Pa	Eur. Pat. Appl., CODEN: EPXXDW	27 pp.	ı
DOCUMENT TYPE:	Patent			
	English	£		
FAMILY ACC. NUM. COUNT: PATENT INFORMATION:	~			
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1340498	A1	20030903	EP 2002-4745	20020301
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EP-1480643		20041201	SP 2003-74336	200302
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distribution coefficient between prasma and brain of 0.3-1.3 bolus injection assay. For the preparation of a medicament fo	rement r	etween plas the prepar	ma and brain of ation of a medic	0.3-1.3 in the mouse
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CAPLUS COPYRIGHT 2007 ACS on STN 2003:511314 CAPLUS Full-text L102 ANSWER 6 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER:

139:85166
Method for producing C1-C6 fragments of epothilones and the derivatives thereof
Rlar, Ulrioh; Berger, Markus; Buchmann, INVENTOR (S): TITLE:

### SN 10/563058 Page 3 of 172 STIC STN SEARCH RESULTS

LANGUAGE: OTHER SOURCE(S): DOCUMENT TYPE:

English CASREACT 142:355075

AB An efficient chiral pool synthesis of the Cl-C6 fragment of epothilones, e.g.
I, starting from readily available (-)-partolactore 1s described.
REFERENCE COUNT:
RECORD. ALL CITATIONS AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Method for producing C1-C15 fragments of epothilones and derivatives thereof
Klar, Ulrich; Buchmann, Barnd;
Schwede, Wolfgang; Skuballa, Merner COPYRIGHT 2007 ACS on STN :29293 CAPLUS Full-text 2005:29293 CAPLUS 142:113814 CAPLUS L102 ANSWER 3 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: TITLE:

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INVENTOR (S):

Schering Aktiengesellschaft, Germany PCT Int. Appl., 48 pp. CODEN: PIXXD2 Patent PATENT ASSIGNEE(S): DOCUMENT TYPE: SOURCE:

German LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

PA	PATENT NO.			KIND.	ن ۵	DATE			APPL	APPLICATION NO.	NO	9	: ;	Ωι	DATE	- 1
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deisopropylidenation/deterrahydropy ranylation with catalytic 4-MeCGH4SO3H in EtOH, silylation with CF3SO2SiMe2CMe3, regioselective desilylation with (t)-camphor-10- sulfonic acid, Swern oxidation with DMSO/(CCI)2 in CH2CI2 and

carbonyl oxidation with NaOC12 in aqueous THF/Me3OOH. The produced C1-C15 epothilone intermediate products can be converted into the intrinsically

catalytic tetrapropylammonium perruthenate, Wittig reaction with [(3S)-3-(2butyldimethyleilyl)oxylheptanal, tetrahydropyranylation, desilylation with BudNF in THF, oxidation in CH2C12 containing N-methylmorpholine N-oxide and

methylbenzothiazol-5- yl)propyl]triphenylphosphonium iodide,

Ħ

dioxane via lithiation and reaction with (2S,6RS)-2-methyl-6-[(tert-

### SN 10/563058 Page 4 of 172 STIC STN SEARCH RESULTS

CASREACT 142:113814; MARPAT 142:113814 NO 2006-554 US 2006-563058 DE 2003-10331004 WO 2004-EP6685 20060403 20070621 4 F NO 2006000554 US 2007142675 PRIORITY APPIN, INFO.: OTHER SOURCE(S):

20060619 20030703 20040619

The invention relates to a method for preparing C1-C15 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1abla (G12)m, m = 2 - 5; R2b, R2b = H, C1-10-alkyl, C2-10-alkwyl, aryl, C7-20-aralkyl; R2aR2b = H, C2-10-alkyl, n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4aR4b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4AR4b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R6, R7 = H, R6R7 = bond, O; G = K:CRB, bi-or tricyclic aryl; R8 = H, halogen, (un)substituted C1-20-alkyl, aryl, C7-20aralkyl; X = 0, (OR23)2, C2-10-alkylene-  $\alpha,\omega$ -dioxy, H(OR9), CR10R11; R23 = C1-20-alkyl; R9 = H, protecting group; R10, R11 = H, C1-10-alkyl, aryl, C7-20-aralkyl; CR10R11 = 5 - to 7-membered carbocycle; R13 = CH2OR13a, CH2-halo, RSC(:V)(CH2)3CH4AR46DC(:W)R3a [V, W = O, (OR23)2, CZ-10-alkylann-a, w-dioxy, H(OB9)), to form a CI-C12 fragment, RSC(:V)(CH2)3CH4AR4DCR3a(0-PG1-C12) fragment, PRC(:V)(CH2)3CH4ARDCR3a(0-RD4), to form a CI-C12 fragment, PRC(:V)(CH2) [RY] = H, protecting group), which is then treated with a Ci3-C15 fragment, PCR20'CH2CH7N'R21 [RY] = H; R20' = halogen, N3, NHR29, OH, O-PG, NR29-PG, CI-20-(perfluoro)alkylsulfonyloxy, (CI-4-alkyl), NO2, C1, Br-substituted banzyloxy, NR29SO2Me, NR35G(:O)Me, R21 = OH, halo, O-PG, P+PhHal = F, CI, Br, I), P(O)(OQ)2 (Q = CI-10-alkyl, Ph), P(:O)PD2; R29 = H, CI-6-alkyll, to form the CI-C15 spothilone intermediate product I. Thus, I [R1a = R1b = R5 = Me, R2a = CH2CH:CH2-B, R2b = R4b = H-a, R3 = H-β, R4a = Me-β, R6R7 = bond, R13 = CO2H, R14 = OSIMe2CMe3-β, R20 = OSIMe2CMe3-a, G = 2-methylbenzothiazol-5- yl, PG = SIMe2CMe3, Z = O] was prepared from (S)-4-(2-methyl-3-oxohept-6-en- 2-yl)-2,2-dimethyl-1,3-CHO, COZRIB, CD-halo, Rija, Ri4a = H, SOZAIK/1, SOZ-aryl, SOZ-aralkyl; RijaRi4a = (CH2)o, CRI5aRi5b; o = 2 - 4; Rijb, Ri4b = H, Cl-10-alkyl; aryl, C7-20-aralkyl; Ri5a, Ribb = H, Cl-10-alkyl, aryl, C7-20-aralkyl; Ri5a, Ribb = H, Cl-10-alkyl, aryl, C7-20-aralkyl; Ri5aRi5b = (CH2)q; q = 3 - 6; R20 = O-PG, NRR29, NR3; Z = 0, H(SR12); R12 = H, PG opporhilones and derive. The procedure comprises the bonding of a Cl-C6 fragment, RijGHZCHRI4CRIaRibC(:0)GHRZaR2b, to a C7-C12 fragment,

### SN 10/563058 Page 1 of 172 STIC STN SEARCH RESULTS

-> file registry ILE 'REGISTRY' ENTERED AT 12:11:27 ON 11 OCT 2007 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT. PLEASE SEE "HELP USAGETERMS" FOR DETAILS. COPYRIGHT (C) 2007 American Chemical Society (ACS) Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem

HIGHEST RN 950149-06-1 HIGHEST RN 950149-06-1 10 OCT 2007 10 OCT 2007 STRUCTURE FILE UPDATES: DICTIONARY FILE UPDATES: New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA : INFORMATION NOW CURRENT THROUGH June 29, 2007

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5.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability  $\phi_{\bf f}$  experimental property data in the original document. For information on property searching in REGISTRY, refer to:

# http://www.cas.org/support/stngen/stndoc/properties.html

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http://www.cas.org/infopolicy.html

L91 AND L92 AND L93 AND L94 KLAR U?/AU BUCHMANN B?/AU SKUBALLA W?/AU SCHWEDE W?/AU. PIU=ON PIU=ON PLU=ON PLU=ON PLU=ON 80 SEA FILE-CAPLUS ABB-ON
116 SEA FILE-CAPLUS ABB-ON
60 SEA FILE-CAPLUS ABB-ON
186 SEA FILE-CAPLUS ABB-ON
24 SEA FILE-CAPLUS ABB-ON d stat que L100 1.91 1.92 1.93 1.94 1.102 î

### SN 10/563058 Page 2 of 172 STIC STN SEARCH RESULTS

=> => d ibib abs L102 tot

Total synthesis and antitumor activity of ZK-EPO: The first fully synthetic epothilon9 in clinical Germany Schering AG, Research Center Eurpoe, Berlin, Gerr Angewandte Chemie, International Edition (2006), Hoffmann, Jens; Lichtner, Rosemarie B. development Klar, Ulrich; Buchmann, Bernd; Schwede, Wolfgang; Skuballa, Werner; Wiley-VCH Verlag GmbH & Co. KGaA 2006:1337456 CAPLUS Full-text 146:229070 CODEN: ACIEF5; ISSN: 1433-7851 CAPLUS COPYRIGHT 2007 ACS on STN English CASREACT 146:229070 45 (47), 7942-7948 L102 ANSWER 1 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: CORPORATE SOURCE: SOURCE: LANGUAGE: OTHER SOURCE(S): PUBLISHER: DOCUMENT TYPE: AUTHOR(S): TITLE:

From about 350 active epothilone analogs synthesized by a highly convergent synthesis, ZK-EPO (I) was chosen for clin. development on the basis of its outstanding preclin. data. This compound exhibits higher activity and efficacy than taxanes, such as pacilitaxel and second-generation epothilones, fast and efficient cellular uptake, no recognition by efflux mechanisms, and an improved therapeutic window.
REFERENCE COUNT: 39 THERE; B

THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Efficient chiral pool synthesis of the C1-C6 fragment Klar, Ulrich; Roehr, Bodo; Kuczynski, Frank; 2005:132732 CAPLUS Full-text COPYRIGHT 2007 ACS on STN of epothilones 142:355075 CAPLUS L102 ANSWER 2 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: AUTHOR(S): TITLE:

Schwede, Wolfgang; Berger, Markus; Skuballa, Werner; Buchmann, Bernd

Research Laboratories of Schering AG, Berlin, 13342, CORPORATE SOURCE: SOURCE:

Synthesis (2005), (2), 301-305 CODEN: SYNTBF, ISSN: 0039-7881 Georg Thieme Verlag

PUBLI SHER:

### SN 10/563058 Page 68 of 69 STIC STN SEARCH RESULTS

D STAT QUE L19

FILE 'BABS' ENTERED AT 15:47:02 ON 11 OCT 2007
D STAT QUE L14

FILE 'ZCAPLUS, BEILSTEIN, BABS' ENTERED AT 15:47:21 ON 11 OCT 2007
L25

25 DUP REM L6 L19 L14 (7 DUPLICATES REMOVED)

ANSWERS '1-18' FROM FILE ZCAPLUS

ANSWERS '19-25' FROM FILE BEILSTEIN

D INTER ARC MITTER 125 1 18

D IBIB ABS HITSTR L25 1-18 D IDE ALLREF L25 19-25

FILE HOME

FILE STNGUIDE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Oct 5, 2007 (20071005/UP).

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1 DICTIONARY FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1

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http://www.cas.org/support/stngen/stndoc/properties.html

FILE ZCAPLUS

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FILE COVERS 1907 - 11 Oct 2007 VOL 147 ISS 16 FILE LAST UPDATED: 10 Oct 2007 (20071010/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

### SN 10/563058 Page 67 of 69 STIC STN SEARCH RESULTS

### => d his full (FILE 'HOME' ENTERED AT 15:09:07 ON 11 OCT 2007) FILE 'STNGUIDE' ENTERED AT 15:22:34 ON 11 OCT 2007 FILE 'REGISTRY' ENTERED AT 15:31:01 ON 11 OCT 2007 STRUCTURE UPLOADED T.1 L2 0 SEA SSS SAM L1 L3 SCREEN 1008 0 SEA SSS SAM L1 AND L3 68 SEA SSS FUL L1 AND L3 SAVE TEMP LAO058STR1CL/A L5 FILE 'ZCAPLUS' ENTERED AT 15:37:30 ON 11 OCT 2007 18 SEA ABB=ON PLU=ON L5 L6 E US2006-563058/APPS 1 SEA ABB=ON PLU=ON US2006-563058/AP D SCA L8 ... 1 SEA ABB=ON PLU=ON L6 AND L7 D SCA FILE 'BEILSTEIN' ENTERED AT 15:40:57 ON 11 OCT 2007 0 SEA SSS SAM L1 L9 L100 SEA SSS SAM L1 AND L3 L11 38 SEA SSS FUL L1 AND L3 26 SEA ABB=ON PLU=ON L11/COM L12 5 SEA ABB=ON PLU=ON L12 AND BABSAN/FA L13 SEL BABSAN FILE 'BABS' ENTERED AT 15:42:39 ON 11 OCT 2007 7 SEA ABB=ON PLU=ON (6300090/BABSAN OR 6630563/BABSAN OR L14 6085475/BABSAN OR 6376421/BABSAN OR 6410256/BABSAN OR 6473119/B ABSAN OR 6597156/BABSAN) FILE 'BEILSTEIN' ENTERED AT 15:43:07 ON 11 OCT 2007 21 SEA ABB=ON PLU=ON L12 NOT L13 14 SEA ABB=ON PLU=ON L15 AND RN/FA L15 L16 FILE 'REGISTRY' ENTERED AT 15:43:45 ON 11 OCT 2007 L17 14 SEA ABB=ON PLU=ON L5 AND BEILSTEIN/LC NOT CAPLUS O SEA ABB=ON PLU=ON L5 AND BEILSTEIN/LC NOT CAPLUS/LC L18 FILE 'BEILSTEIN' ENTERED AT 15:44:11 ON 11 OCT 2007 L19 7 SEA ABB=ON PLU=ON L15 NOT L16 252 SEA ABB=ON PLU=ON KLAR U?/AU L20 351 SEA ABB=ON PLU=ON BUCHMANN B?/AU 436 SEA ABB=ON PLU=ON SCHWEDE W?/AU L22 369 SEA ABB=ON PLU=ON SKUBALLA W?/AU L23 0 SEA ABB=ON PLU=ON L19 AND (L20 OR L21 OR L22 OR L23) D-COST The state of the s

FILE 'REGISTRY' ENTERED AT 15:46:28 ON 11 OCT 2007

FILE 'ZCAPLUS' ENTERED AT 15:46:31 ON 11 OCT 2007 D STAT QUE L6

FILE 'BEILSTEIN' ENTERED AT 15:46:51 ON 11 OCT 2007

### SN 10/563058 Page 66 of 69 STIC STN SEARCH RESULTS

### Field Availability:

Code	Name	Occurrence	2
BRN	Beilstein Records	1	
MF	Molecular Formula	1	
FW	Formular Weight	$oldsymbol{1}_{i_1,i_2,i_3}$ , $oldsymbol{1}_{i_1,i_2,i_3}$ , $oldsymbol{1}_{i_1,i_2,i_3}$	
LN	Lawson Number	. 3	
FS	File Segment	. 1	
CTYPE	Compound Type	1	
CONSID	Constitution ID	1	
TAUTID	Tautomer ID	1	
BSO.	Beilstein Citation	. 1	
DED	Entry Date	1	
DUPD	Update Date	1	
NMR	Nuclear Magnetic Resona		

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
========	======================================	========
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

### All References:

ALLREF

1. Aberhart et al., J.Chem.Soc.Perkin Trans.1, CODEN: JCPRB4, <1974>, 816,823

### SN 10/563058 Page 65 of 69 STIC STN SEARCH RESULTS

<u> </u>		==
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	6
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1.
CDER	Chemical Derivative	1

### This substance also occurs in Reaction Documents:

Code	Name	Occurrence
	=== <b>====================</b> =============	
RX	Reaction Documents	1
RXPRO:	- Substance is Reaction Product	· 1

### All References:

ALLREF

1. Fehr, T. et al., J.Chem.Soc.Perkin Trans.1, CODEN: JCPRB4, <1974>, 836-847

### L25 ANSWER 25 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN): 1677640 C40 H60 D2 O21 Molec. Formula (MF): 880.93 Molecular Weight (MW): Lawson Number (LN): 17586, 1155, 680 Stereo compound File Segment (FS): heterocyclic Compound Type (CTYPE): Constitution ID (CONSID): 1560573 Tautomer ID (TAUTID): 1638549 Beilstein Citation (BSO): 1988/11/30 Entry Date (DED): 1990/02/07 Update Date (DUPD):

### SN 10/563058 Page 64 of 69 STIC STN SEARCH RESULTS

RX Reaction Documents 1

RXPRO

Substance is Reaction Product

1

All References:

ALLREF

 Aberhart et al., J.Chem.Soc.Perkin Trans.1, CODEN: JCPRB4, <1974>, 816,823

L25 ANSWER 24 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):

1677845

Chemical Name (CN):

2-butyl-18-(3,4-dimethoxy-5-methoxymethyltetrahydro-furan-2-yloxy)-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-

dimethyl-tritriacont-16-enoic acid

1-(2-hydroxy-1-methyl-ethyl)-3-methoxy-2methyl-6-(N, N', N'-trimethyl-quanidino)-

hexyl ester

Autonom Name (AUN):

2-butyl-18-(3,4-dimethoxy-5-methoxymethyltetrahydro-furan-2-yloxy)-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16dimethyl-tritriacont-16-enoic acid

1-(2-hydroxy-1-methyl-ethyl)-3-methoxy-2methyl-6-(N,N',N'-trimethyl-guanidino)-

hexyl ester C71 H139 N3 O19

heterocyclic

Molec. Formula (MF):

Molecular Weight (MW): 1338.89

Lawson Number (LN):

17586, 3238, 2817, 2294, 1762, 289 Stereo compound

File Segment (FS): Compound Type (CTYPE): Constitution ID (CONSID):

1561576 1636624

Tautomer ID (TAUTID): Beilstein Citation (BSO):

5-17 1988/11/30 Entry Date (DED): 1991/03/25 Update Date (DUPD):

Field Availability:

Code Name Occurrence

### SN 10/563058 Page 63 of 69 STIC STN SEARCH RESULTS

1. Chakraborty, T. K.; Dutta, S., Tetrahedron Lett., CODEN: TELEAY, 39(1-2), <1998>, 101-104; BABS-6085475

### L25 ANSWER 23 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

1965671 Beilstein Records (BRN): heptadecane-1, 3, 5, 7, 9, 11, 16-heptaol Chemical Name (CN): heptadecane-1,3,5,7,9,11,16-heptaol Autonom Name (AUN): Molec. Formula (MF): C17 H36 O7 352.47 Molecular Weight (MW): 687 Lawson Number (LN): Compound Type (CTYPE): acyclic Constitution ID (CONSID): 1838397 Tautomer ID (TAUTID): 1903620 Beilstein Citation (BSO): 5-01 1989/06/29 Entry Date (DED): 1997/12/03 Update Date (DUPD):

### Field Availability:

7 Mg 20

Code	Name	Occuri	ence
BRN	Beilstein Records		1
BPR	Beilstein Preferred RN		1
RN	CAS Registry Number		1
CN	Chemical Name		1
AUN	Autonomname		1
MF	Molecular Formula		1
FW	Formular Weight		1
LN	Lawson Number		1
CTYPE	Compound Type		1
CONSID	Constitution ID		1
TAUTID	Tautomer ID		1
BSO	Beilstein Citation		1 .
DED	Entry Date		1
DUPD	Update Date		1
IR	Infrared Spectrum	rusi.	1
MP	Melting Point		1
MS	Mass Spectrum		1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
=======		

- 120 at 15 
### SN 10/563058 Page 62 of 69 STIC STN SEARCH RESULTS

Chemical Name (CN): 12-benzyloxy-7-(tert-butyl-dimethylsilanyloxy)-3-hydroxy-4,4,6,8-tetramethyl-5-oxo-dodecanoic acid tert-butyl ester 12-benzyloxy-7-(tert-butyl-dimethyl-Autonom Name (AUN): silanyloxy)-3-hydroxy-4,4,6,8-tetramethyl-5-oxo-dodecanoic acid tert-butyl ester C33 H58 O6 Si Molec. Formula (MF): Molecular Weight (MW): 578.90 5228, 3798, 3777, 2672, 318 Lawson Number (LN): File Segment (FS): Stereo compound Compound Type (CTYPE): isocyclic 6834281 Constitution ID (CONSID): Tautomer ID (TAUTID): 7583399 Beilstein Citation (BSO): 6-06 Entry Date (DED): 1998/11/09 Update Date (DUPD): 1998/11/09

### Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	. 1
MF	Molecular Formula	. 1
FW	Formular Weight	1
LN	Lawson Number	• 5
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	.1
DUPD	Update Date	1

### This substance also occurs in Reaction Documents:

Code	Name		ina .		4	Occurrence
========		===	=======	=======	==:	=== <b>==</b> =====
RX	Reaction	Doc	uments			. 2
RXREA	Substance	is	Reaction	Reactant		1
RXPRO	Substance	is	Reaction	Product		1

### All References:

ALLREF

### Field Availability:

Code	Name	Occurrenc	
======			
BRN	Beilstein Records	1	
CN	Chemical Name	1	
AUN	Autonomname	. 1	
MF	Molecular Formula	1	
FW	Formular Weight	1	
LN	Lawson Number	3	
FS	File Segment	1	
CTYPE	Compound Type	1	
CONSID	Constitution ID	1	
TAUTID	Tautomer ID	1	
DED	Entry Date	1	
DUPD	Update Date	1	
	-		

### This substance also occurs in Reaction Documents:

Code	Name	Occurrence
=======		
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	1
RXPRO	Substance is Reaction Product	1

### All References: ALLREF

- Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6591064
- 2. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron-Lett., CODEN: TELEAY, 45(9), <2004>, 1945 1948; BABS-6441824;

### L25 ANSWER 22 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):

7955235

### Field Availability:

Code	Name	Occurrence	
=======			
BRN	Beilstein Records	1	
CN ·	Chemical Name	1	
AUN	Autonomname	1	
MF	Molecular Formula	1	
FW	Formular Weight	1	
LN	Lawson Number	. 4	
FS	File Segment	1	
CTYPE	Compound Type	1	
CONSID	Constitution ID	1	
TAUTID	Tautomer ID	1	
DED	Entry Date	1	
DUPD	Update Date	· 1	

### This substance also occurs in Reaction Documents:

Code	Name	Occurrence
=======		=========
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	. 1
RXPRO	Substance is Reaction Product	. 1

### All References:

### ALLREF

- Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6591064
- Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6441824

### L25 ANSWER 21 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):	9738862
Chemical Name (CN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-
	4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid
Autonom Name (AUN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-
	4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic
	acid
Molec. Formula (MF):	C29 H58 O6 Si2
Molecular Weight (MW):	558.94
Lawson Number (LN):	3798, 3777, 2674
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	acyclic
Constitution ID (CONSID):	8203590
Tautomer ID (TAUTID):	9128603
<pre>Entry Date (DED):</pre>	2004/10/23
Update Date (DUPD):	2007/02/05

### SN 10/563058 Page 59 of 69 STIC STN SEARCH RESULTS

CTYPE	Compound Type	•	•	. 1
CONSID	Constitution ID			1
TAUTID	Tautomer ID			1
DED	Entry Date			1
DUPD	Update Date			1

### This substance also occurs in Reaction Documents:

Code	Name	Occurrence
=========		
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	1
RXPRO	Substance is Reaction Product	1

### All References:

### ALLREF

- Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6591064
- 2. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 1948; BABS-6441824

### L25 ANSWER 20 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN): 9738952 3,7-bis-(tert-butyl-dimethyl-silanyloxy)-Chemical Name (CN): 4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid methyl ester 3,7-bis-(tert-butyl-dimethyl-silanyloxy)-Autonom Name (AUN): 4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid methyl ester C30 H60 O6 Si2 Molec. Formula (MF): 572.97 Molecular Weight (MW): 3798, 3777, 2674, 289 Lawson Number (LN): File Segment (FS): Stereo compound Compound Type (CTYPE): acyclic Constitution ID (CONSID): 8203696 Tautomer ID (TAUTID): 9128457 2004/10/23 Entry Date (DED): Update Date (DUPD): 2007/02/05

### L25 ANSWER 19 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN): 9747518 Chemical Name (CN): 3,7-bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid 2-methyl-3-(2-methyl-thiazol-4-yl)-1-(2-oxo-ethyl)-allyl ester Autonom Name (AUN): 3,7-bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid 2-methyl-3-(2-methyl-thiazol-4-yl)-1-(2-oxo-ethyl)-allyl ester C39 H69 N O7 S Si2 Molec. Formula (MF): Molecular Weight (MW): 752.21 Lawson Number (LN): 31322, 3798, 3777, 2674 File Segment (FS): Stereo compound Compound Type (CTYPE): heterocyclic Constitution ID (CONSID): 8211765 Tautomer ID (TAUTID): 9136618 Entry Date (DED): 2004/10/23 Update Date (DUPD): 2007/02/05

### Field Availability:

Code	Name	Occurrence
======	Beilstein Records	1
BRN CN	Chemical Name	<u>.</u> 1
AUN	Autonomname	1
MF	Molecular Formula	
FW	Formular Weight	1
LN	Lawson Number	4
FS	File Segment	1

### SN 10/563058 Page 57 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

RN 53294-58-9 ZCAPLUS

CN 1,2,3,5,7,9,11,16-Heptadecaneoctol (9CI) (CA INDEX NAME)

RN 53294-63-6 ZCAPLUS

CN 1,2,3,5,7,9,11,16-Heptadecaneoctol, octaacetate (9CI) (CA INDEX NAME)

RN 53294-64-7 ZCAPLUS

CN: 1,3,5,7,9,14-Pentadecanehexol (9CI) (CA INDEX NAME)

RN 53294-65-8 ZCAPLUS

CN 1,3,5,7,9,14-Pentadecanehexol, hexaacetate (9CI) (CA INDEX NAME)

RN 53294-66-9 ZCAPLUS

CN 1,3,5,7,9,11,16-Heptadecaneheptol, heptaacetate (9CI) (CA INDEX NAME)

### SN 10/563058 Page 56 of 69 STIC STN SEARCH RESULTS

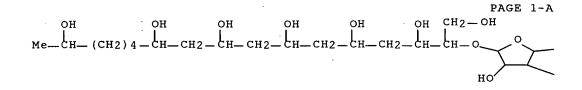
- The structures of secopyrimycins A [MeO2CCHBuCH(OH)CHMe(CH2)2[CH(OH)(CH2)3]2[CH(OH)]2Me], B (I), and C, [AcNH(CH2)3[CH(OH)CHMe]2 CH2OH] were detd.from their high resolution mass spectra and/or those of their simplederivs. and chemical degradation products.
- IT 54799-27-8

RL: PRP (Properties)

(mol. structure of, mass spectrum in relation to)

RN 54799-27-8 ZCAPLUS

CN 1,3,5,7,9,11,16-Heptadecaneheptol, 2-( $\alpha$ -D-arabinofuranosyloxy)-(9CI) (CA INDEX NAME)



PAGE 1-B

\_\_\_\_CH2 - OH

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L25 ANSWER 18 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1974:437769 ZCAPLUS Full-text

DOCUMENT NUMBER:

81:37769

TITLE:

Constitution of primycin. I. Characterization,

functional groups, and degradation to the

secoprimycins

AUTHOR(S):

Aberhart, John; Jain, Rup C.; Fehr, Theo; De Mayo,

Paul; Szilagyi, Imre

CORPORATE SOURCE:

Dep. Chem., Univ. West. Ont., London, ON, Can.

SOURCE:

Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999)

(1974), (7), 816-26

CODEN: JCPRB4; ISSN: 0300-922X

DOCUMENT TYPE:

Journal English

LANGUAGE:

GI For diagram(s), see printed CA Issue.

AB The proposed structure of primycin (I) was determined mainly from the chemical and spectral data-of its degradation products.

IT 53294-56-7P 53294-58-9P 53294-63-6P 53294-64-7P 53294-65-8P 53294-66-9P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of)

RN 53294-56-7 ZCAPLUS

CN 1,3,5,7,9,11,16-Heptadecaneheptol, 2-[(2,3,5-tri-O-acetyl- $\alpha$ -D-arabinofuranosyl)oxy]-, heptaacetate (9CI) (CA INDEX NAME)

### SN 10/563058 Page 55 of 69 STIC STN SEARCH RESULTS

arabinofuranosyl)oxy]-, 6-[[(dimethylamino)iminomethyl]methylamino]-1-(2hydroxy-1-methylethyl)-3-methoxy-2-methylhexyl ester, monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A

HC1

PAGE 1-B

L25 ANSWER 17 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1974:436929 ZCAPLUS Full-text

DOCUMENT NUMBER:

81:36929

TITLE:

Constitution of primycin. II. Mass spectra of the

secoprimycins

AUTHOR(S):

Gracey, D. E. Fergus; Baczynskyj, Lubomir; Martin,

Trevor I.; MacLean, David B.

CORPORATE SOURCE:

Dep. Chem., McMaster Univ., Hamilton, ON, Can.

SOURCE:

Journal of the Chemical Society, Perkin Transactions

1: Organic and Bio-Organic Chemistry (1972-1999)

(1974), (7), 827-36

CODEN: JCPRB4; ISSN: 0300-922X

DOCUMENT TYPE:

Journal

LANGUAGE:

English

For diagram(s), see printed CA Issue.

PAGE 1-B

**∼**OMe

RN 53294-05-6 ZCAPLUS

CN 16-Tritriacontenoic acid, 2-butyl-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-32-oxo-18-[(2,3,5-tri-O-methyl- $\alpha$ -D-arabinofuranosyl)oxy]-, methyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

PAGE 1-B

RN 53294-53-4 ZCAPLUS

CN α-D-Arabinofuranoside, 2,4,6,8,10-pentamethoxy-15-(methoxy-d3)-1-(methoxy-d3-methyl)hexadecyl 2,3,5-tri-0-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 53503-23-4 ZCAPLUS

CN 16-Tritriacontenoic acid, 2-butyl-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-18-[(2,3,5-tri-O-methyl- $\alpha$ -D-

### SN 10/563058 Page 53 of 69 STIC STN SEARCH RESULTS

RN 53294-03-4 ZCAPLUS

CN 16-Tritriacontenoic acid, 32-(acetyloxy)-2-butyl-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-18-[(2,3,5-tri-O-methyl- $\alpha$ -D-arabinofuranosyl)oxy]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-B

**∽**OMe

RN 53294-04-5 ZCAPLUS

CN 16-Tritriacontenoic acid, 2-butyl-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-18-[(2,3,5-tri-O-methyl- $\alpha$ -D-arabinofuranosyl)oxy]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

### SN 10/563058 Page 52 of 69 STIC STN SEARCH RESULTS

DOCUMENT TYPE:

Journal

LANGUAGE:

ĠΙ

AGE: English
For diagram(s), see printed CA Issue.

AB Methylation of primycin (I) gave, after chromatog., the trimethylated urea and guanidine derivs. (II and III). The structure of I was determined by a spectral study of the ozonolysis products of II and III and their degradation products.

IT 53293-97-3P 53293-98-4P 53293-99-5P 53294-00-1P 53294-03-4P 53294-04-5P 53294-05-6P 53294-53-4P 53503-23-4P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of)

RN 53293-97-3 ZCAPLUS

CN α-D-Arabinofuranoside, 15-hydroxy-1-(hydroxymethyl)-2,4,6,8,10pentamethoxyhexadecyl 2,3,5-tri-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 53293-98-4 ZCAPLUS

CN  $\alpha$ -D-Arabinofuranoside, 15-(acetyloxy)-1-[(acetyloxy)methyl]-2,4,6,8,10-pentamethoxyhexadecyl 2,3,5-tri-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 53293-99-5 ZCAPLUS

CN 1,2,16-Heptadecanetriol, 3,5,7,9,11-pentamethoxy- (9CI) (CA INDEX NAME)

RN 53294-00-1 ZCAPLUS

CN Hexadecanal, 15-hydroxy-2,4,6,8,10-pentamethoxy- (9CI) (CA INDEX NAME)

### SN 10/563058 Page 51 of 69 STIC STN SEARCH RESULTS

RN. 197634-37-0 ZCAPLUS

CN 4,15-Dioxa-3,16-disilaoctadecan-7-one, 5-(2-hydroxyethyl)-2,2,3,3,6,6,8,10,17,17-decamethyl-16,16-diphenyl-9-(phenylmethoxy)-, [5S-(5R\*,8S\*,9R\*,10R\*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-39-2 ZCAPLUS

CN Dodecanoic acid, 3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-12-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,4,6,8-tetramethyl-5-oxo-7-(phenylmethoxy)-, [3S-(3R\*,6S\*,7R\*,8R\*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L25 ANSWER 16 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1974:463919 ZCAPLUS Full-text

DOCUMENT NUMBER:

81:63919

TITLE:

Constitution of primycin. III. Degradation of methylated primycin, and the structure of primycin

AUTHOR(S):

methylated primycin, and the structure of primycin Fehr, Theo; Jain, Rup C.; De Mayo, Paul; Motl, O.; Szilagyi, Imre; Baczynskyj, Lubomir; Gracey, D. E. Fergus; Holland, Herbert L.; MacLean, David B.

CORPORATE SOURCE:

Dep. Chem., Univ. West. Ont., London, ON, Can.

SOURCE:

Journal of the Chemical Society, Perkin Transactions

1: Organic and Bio-Organic Chemistry (1972-1999)

(1974), (7), 836-47

CODEN: JCPRB4; ISSN: 0300-922X

## SN 10/563058 Page 50 of 69 STIC STN SEARCH RESULTS

RN 197634-31-4 ZCAPLUS

CN 3-Decanone, 2-(2,2-dimethyl-1,3-dioxan-4-yl)-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,4,6-trimethyl-5-(phenylmethoxy)-, [4S-[4R\*(4S\*,5R\*,6R\*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-33-6 ZCAPLUS

CN 5-Dodecanone, 12-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1,3-dihydroxy-4,4,6,8-tetramethyl-7-(phenylmethoxy)-, [3S-(3R\*,6S\*,7R\*,8R\*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-35-8 ZCAPLUS

CN 4,17-Dioxa-3,18-disilaeicosan-9-one, 7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,2,3,3,8,8,10,12,19,19-decamethyl-18,18-diphenyl-11-(phenylmethoxy)-, [7S-(7R\*,10S\*,11R\*,12R\*)]- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 49 of 69 STIC STN SEARCH RESULTS

IT 197634-28-9P 197634-29-0P 197634-30-3P 197634-31-4P 197634-33-6P 197634-35-8P 197634-37-0P 197634-39-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediates in the total synthesis of epothilones A and B)

RN 197634-28-9 ZCAPLUS

CN 3-Decanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-29-0 ZCAPLUS

CN 3-Decanone, 2-(2,2-dimethyl-1,3-dioxan-4-yl)-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6-trimethyl-5-(phenylmethoxy)-,
[4S-[4R\*(4S\*,5R\*,6R\*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-30-3 ZCAPLUS

CN 3-Decanone, 2-(2,2-dimethyl-1,3-dioxan-4-yl)-10-hydroxy-2,4,6-trimethyl-5-(phenylmethoxy)-, [4S-[4R\*(4S\*,5R\*,6R\*)]]- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 48 of 69 STIC STN SEARCH RESULTS

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                                             US 1999-344713
                                                                 A3 19990625
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OTHER SOURCE(S):

CASREACT 127:346234

GΙ

Intermediates, e.g. 2-(2,2-dimethyl-1,3-dioxan-4-yl)-2-methyl-3-pentanone, 6-AΒ [(tert-butyldimethylsilyl)oxy]-2-methylhexanal, (S,4E)-3-benzyloxy-1- (tertbutyldimethylsilyloxy)-4-methyl-5-(2-ethyl-thiazol-4-yl)-4-pentene (I), (4S,6S)-10(tert-butyldimethylsilyloxy)-2-(2,2-dimethyl-1,3-dioxan-4-yl)-5hydroxy-2,4,6-trimethyl-3-decanone (II) and (3S,6R,7S,8S)-7- benzyloxy-3-(tert-butyldimethylsilyloxy) -12-(tert-butyldiphenylsilyloxy) - 4,4,6,8tetramethyl-5-oxododecanoic acid, in the total synthesis of epothilones A and B are described. Epothilones A and B are natural products,.

IT 197634-08-5P

> RL: PNU (Preparation, unclassified); PREP (Preparation) (intermediates in the total synthesis of epothilones A and B)

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RN197634-08-5 ZCAPLUS

Dodecanoic acid, 12-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,7-dihydroxy-CN 4.4.6.8-tetramethyl-5-oxo-, methyl ester,  $[3S-(3R^*,6S^*,7R^*,8R^*)]-(9CI)$ (CA INDEX NAME)

The title compds. [I; II; III; R1, R2 = H, alkyl, aryl, aralkyl; R3 = CH2OH, CH2OR; R4 = OH, OR; R = CR7R8; R7, R8 = H, alkyl, aryl, or R7R8 = (CH2)n; n = 2-6; R5, R6 = H, alkyl, aralkyl, or R5R6 = (CH2)m; m = 2-5; R9, R10 = H, protecting group; R11 = H, protecting group] including all the stereoisomers and their mixts. are prepared E.g., title compound (S)-III [R5 = R6 = Me, R9 = R11 = H, R10 = TBDPS] was prepared in 6 steps from D-(-)-pantolactone via reaction with 3,4-dihydro-2H-pyran, hydride reduction, Wittig reaction with methyltriphenylphosphonium bromide, protection of OH with TBDPS-Cl, deternallydropyranyl, and reduction with borane-THF.

IT 197634-28-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of new C1-C6-fragments and application for synthesis of epothilone and epothilone derivs.)

RN 197634-28-9 ZCAPLUS

CN 3-Decanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L25 ANSWER 15 OF 25 ZCAPLUS CO ACCESSION NUMBER: 1997:708

ZCAPLUS COPYRIGHT 2007 ACS on STN 1997:708545 ZCAPLUS Full-text

DOCUMENT NUMBER: 127:346234

CUMENI NUMBER: 127:34023

TITLE: Intermediate products within the total synthesis of

Epothilones A and B

INVENTOR(S): Schinzer, Dieter; Limberg, Anja; Boehm, Oliver M.

CODEN: GWXXAW

PATENT ASSIGNEE(S): Schering A.-G., Germany

SOURCE: Ger., 14 pp.

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND DATE	APPLICATI	ON NO.	DATE
DE 19636343	ci 19971	023 DE 1996-1	9636343	19960830
DE 19645361	A1 19980	430 DE 1996-1	9645361	19961028
WO 9808849	A1 19980	305 WO 1997-D	E111	19970115
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FI, GB, GE,	HU, IL, IS,	JP, KE, KG, KP,	KR, KZ, LK,	LR, LS, LT,
LU, LV, MD,	MG, MK, MN,	MW, MX, NO, NZ,	PL, PT, RO,	RU, SD, SE,
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KZ, MD, RU,	TJ, TM			
RW: KE, LS, MW,	SD, SZ, UG,	AT, BE, CH, DE,	DK, ES, FI,	FR, GB, GR,

## SN 10/563058 Page 46 of 69 STIC STN SEARCH RESULTS

TITLE:

New (C1-C6)-fragments, method for their preparation and their application for synthesis of epothilone and

epothilone derivatives

INVENTOR(S):

Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner;

Buchmann, Bernd; Schirner, Michael

PATENT ASSIGNEE(S):

Schering A.-G., Germany

SOURCE:

Ger. Offen., 18 pp.

CODEN: GWXXBX

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

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	19735				A1 19990211				DE	1997-	1973	5578		1	9970	809					
CA	22996	508			A1	A1 1999		.9990218			CA 1998-2299608					19980810					
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WO	99076	592			<b>A</b> 3		1999	0514													
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OTHER S	OURCE	(S):			CAS	REAC	T 13	0:16	8164	; M	IARPAT	130	:168	164							

R5 R6 R2

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$$R^{5}$$
  $R^{6}$   $OR^{10}$   $OR^{9}$   $II$ 

# SN 10/563058 Page 45 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

RN 220774-78-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4S,5R,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-80-1 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(phenylmethyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7R,8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. --

L25 ANSWER 14 OF 25 ACCESSION NUMBER:

ZCAPLUS COPYRIGHT 2007 ACS on STN 1999:116659 ZCAPLUS <u>Full-text</u> 130:168164

## SN 10/563058 Page 44 of 69 STIC STN SEARCH RESULTS

RN 220774-61-8 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-62-9 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(phenylmethyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-76-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(phenylmethyl)-5[(tetrahydro-2H-pyran-2-yl)oxy]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 43 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

RN 220774-58-3 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-59-4 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-60-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(phenylmethyl)-5[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

# SN 10/563058 Page 42 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

RN 220774-21-0 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-22-1 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-4-ethyl-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-23-2 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-8-ethyl-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 41 of 69 STIC STN SEARCH RESULTS

melanoma, and acute lymphocytic and myelocytic leukemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, and for better tolerability of, medical implants, the derivs. can be introduced into or applied to polymeric materials. The compds. provided for in the invention can be used alone or, to achieve additive or synergistic effects, in combination with other principles and substance categories used in tumor therapy.

IT 220775-76-8

RL: RCT (Reactant); RACT (Reactant or reagent) (preparation of epothilone derivs. as antitumor agents)

RN 220775-76-8 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,8,10-trimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 220774-19-6P 220774-20-9P 220774-21-0P 220774-22-1P 220774-23-2P 220774-58-3P 220774-59-4P 220774-60-7P 220774-61-8P 220774-62-9P 220774-76-5P 220774-78-7P 220774-80-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of epothilone derivs. as antitumor agents)

RN 220774-19-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-20-9 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 40 of 69 STIC STN SEARCH RESULTS

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DE	1973	5578			A1	199	90211	DE	1997-	-1973	5578			19970	809
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DE	1974	9717			A1	199	90506	DE	1997-	-1974	9717			19971	031
DE	1975	1200			A1	199	90520	DE	1997-	-1975	1200			19971	113
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CA	2299	608			A1	199	90218	CA	1998-	-2299	608			19980	810
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IN	1908	05			A1		30823		1998-	-DE34	13			19981	
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IN	2002	DE013	305		Α	200	50311		2002-					20021	
PRIORITY	Y APP	LN.	INFO	.:					1997-				A	19970	
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									1997-				A	19970	
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									1997-				A	19971	
									1997-				A	19971	
									1998-				A	19980	
					•			WO	1998-	-EP50	64		W	19980	810

OTHER SOURCE(S):

MARPAT 130:196529

GI

AB Epothilone derivs. of formula I  $[X = 0, alkylene-\alpha, \omega-dioxy, two alkoxy groups,$ etc.; Y = O, H2; Z = O, (H, OH), (H, protected OH); R1a, R1b = H, alkyl, aryl, aralkyl, or together = (CH2)m where m = 2, 3, 4, 5; R2a, R2b = H, alkyl, aryl, aralkyl, or together = (CH2)n where n = 2, 3, 4, 5; when D-E = CH2CH2 or when Y = O, R2a or R2b may not be H/Me; R3 = H, alkyl, aryl, aralkyl; R4a, R4b = H, alkyl, aryl, aralkyl, or together = (CH2)p where p = 2, 3, 4, 5; D-E = CH2CH2,CH:CH, C.tplbond.C, 2,3-oxiranediyl, CH(OH)CH(OH), CH(OH)CH2; R5 = H, alkyl, aryl, aralkyl; R6, R7 = H, together = a saturated bond or O; R8 = H, alkyl, Law rimaryl, aralkyl all of which may be substituted] are prepared. Thus, the title compds. (4S,7R,8S,9S,13E,16S(E)) - and (4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-7- ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-oxa-5,5,9,13tetramethylcyclohexadec-13-en-2,6-dione (II) were prepared in many steps. The new compds. interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumors, such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant

# SN 10/563058 Page 39 of 69 STIC STN SEARCH RESULTS

220774-23-2 ZCAPLUS RN

2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-8-ethyl-6,10dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L25 ANSWER (13 OF 25

ZCAPLUS COPYRIGHT 2007 ACS on STN 1999:126888 ZCAPLUS

ACCESSION NUMBER: DOCUMENT NUMBER:

130:196529

TITLE:

Preparation of new epothilone derivatives as

pharmaceutical agents

INVENTOR(S):

Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner;

Full-text

Buchmann, Bernd; Schirner, Michael

PATENT ASSIGNEE(S):

Schering Aktiengesellschaft, Germany

SOURCE:

PCT Int. Appl., 185 pp. Lagrange of the persons of the property of the person of the p

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PAT	CENT	NO.			KIN	D :	DATE		i	APPL	ICAT:	ION I	NO.		D	ATE	
						-											
WO	9907	692			A2		1999	0218	Ţ	WO 1	998-	EP50	64		1	9980	8,10
WO	9907	692			A3		1999	0514									
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		ΚZ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,
		PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	TM,	TR,	TT,	UA,	UG,
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		CM,	GΑ,	GN,	GW,	ML,	MR,	NE,	SN,	TD,	TG						
DE	1973	5574			A1		1999	0211		DE 1	997-	1973	5574		1	9970	809

5.000.00

#### SN 10/563058 Page 38 of 69 STIC STN SEARCH RESULTS

RN 220774-20-9 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-21-0 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-22-1 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-4-ethyl-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Ι

New epothilone derivs. I (Rla, Rlb = R2a, R2b = same or different H, alkyl, AB aryl, aralkyl or (CH2)m,n m, n = 2-5; R3 = H, alkyl, aryl, aralkyl; R4a,R4b =same or different H, alkyl, aryl, aralkyl or (CH2)p = 2-5, CH2CH2, CH=CH, C.tplbond.C, epoxy, CH(OH)CH(OH), CH(OH)CH2; D-E = a group; R5 = H, alkyl, aryl, aralkyl; R6,R7 = H, bond, O; R8 = H, alkyl, aryl, aralkyl; X = O, OR23 alkylene- $\alpha$ ,- $\omega$ -dioxy group straight or branched, OR9 or the CR10R11 group where R23 = alkyl, R9 = H or protecting group and R10, R11 = same or different H. alkyl, aryl, aralkyl or R10,R11 = together with methylene are a 5-7 membered carbocyclic ring; Y = O or two H; Z = O or H/OR12 and R12 = H or a protecting group) were prepared Thus E- and Z-II were prepared via a multistep synthesis. I cooperate with tubulin by stabilizing formed microtubuli. able phase specifically to affect the cell division and are suitable for the treatment of malignant ovarian, stomach, colon, adeno, breast, lung, head and neck tumors, malignant melanomas, acute lymphocytic and myelocytic leukemia. Derivs. of I are suitable for use in anti-angiogenic therapy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). \*Incorder to prevent uncontrolled cell proliferations and to improve the compatibility of medical implants I can be applied or incorporated into polymeric materials. I can be used alone or to achieve additive or synergistic effects in combination with further principles and substance classes applicable in tumor therapy.

IT 220774-19-6P 220774-20-9P 220774-21-0P

220774-22-1P 220774-23-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of new epothilone derivs. and their pharmaceutical uses)

RN 220774-19-6 ZCAPLUS

CN

3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

## SN 10/563058 Page 36 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

IT 303154-57-6₽

> RL: SPN (Synthetic preparation); PREP (Preparation) (6-alkenyl and 6-alkynyl derivs. of epothilone)

RN 303154-57-6 ZCAPLUS

3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dioxCN dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L25 ANSWER 12 OF 25

ZCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2000:738730 ZCAPLUS Full-text 133:309795 . . .

DOCUMENT NUMBER:

TITLE: Preparation of new epothilone derivatives and their

pharmaceutical uses

Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; INVENTOR(S):

Buchmann, Bernd; Schirner, Michael

PATENT ASSIGNEE(S): Schering A.-G., Germany

SOURCE: Ger. Offen., 74 pp.

CODEN: GWXXBX DOCUMENT TYPE: Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19908767	A1	20001019	DE 1999-19908767	19990218
PRIORITY APPLN. INFO.:			DE 1999-19908767	19990218
OTHER SOURCE(S):	MARPAT	133:309795		
GI				

## SN 10/563058 Page 35 of 69 STIC STN SEARCH RESULTS

RN 303154-58-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-59-8 ZCAPLUS

CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-60-1 ZCAPLUS

CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 34 of 69 STIC STN SEARCH RESULTS

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PRIORITY APPLN. INFO.:
                                            DE 1999-19921086
                                            DE 1999-19954228
                                                                A 19991104
                                                                A 20000309
                                            DE 2000-10013363
                                            DE 2000-10015836
                                                                A 20000327
                                                                A3 20000501
                                            JP 2000-615619
                                            WO 2000-IB657
                                                                W 20000501
                                            IN 2001-MN1305
                                                                A3 20011019
                                            US 2002-979939
                                                                A3 20020606
OTHER SOURCE(S):
                         MARPAT 133:321769
     The title compds. were prepared by various combinations of 3 fragments making
AΒ
     up the mols. Thus, [4S,7R,8S,9S,13Z,16S(E)]-4,8-dihydroxy-16-[1- methyl-2-(2-
     pyridyl)ethenyl]-1-oxa-5,5,9,13-tetramethyl-7-(3-butynyl)-13- cyclohexadecene-
      2.6-dione was prepared in several steps starting from (4S)-4-(2-methyl-1-oxo-
     2-propyl)-2,2-dimethyl[1,3]dioxane and 5-(trimethylsilyl)-4-pentynylmagnesium
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bromide. IT 303154-56-5P 303154-58-7P 303154-59-8P 303154-60-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(6-alkenyl and 6-alkynyl derivs. of epothilone)

RN 303154-56-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 33 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

#### IT 303154-57-6P

RL: SPN (Synthetic preparation); PREP (Preparation) (preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilone derivs. and their use in pharmaceutical prepns.)

303154-57-6 ZCAPLUS RN

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dioxan-4-[[(1,1-dioxandimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 11 OF 25

ACCESSION (NUMBER:

DOCUMENT NUMBER:

PATENT ASSIGNEE(S):

TITLE:

SOURCE:

INVENTOR(S):

133:321769

6-Alkenyl and 6-alkynyl derivatives of epothilone Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Hoffmann, Jens; Lichtner, Rosemarie

Schering A.-G., Germany

ZCAPLUS COPYRIGHT 2007 ACS on STN

2000:772379 ZCAPLUS Full-text

Ger. Offen., 18 pp.

CODEN: GWXXBX

DOCUMENT TYPE:

LANGUAGE:

Patent German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19921086	A1	20001102	DE 1999-19921086	19990430
CA 2371226	A1	20001109	CA 2000-2371226	20000501
WO 2000066589	A1	20001109	WO 2000-IB657	20000501

## SN 10/563058 Page 32 of 69 STIC STN SEARCH RESULTS

RN 303154-58-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-59-8 ZCAPLUS

CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-60-1 ZCAPLUS

CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)-(9CI) (CA INDEX NAME)

#### SN 10/563058 Page 31 of 69 STIC STN SEARCH RESULTS

DE 1999-19954228 A1 19991104 DE 2000-10015836 A1 20000327 DE 2000-10013363 Α 20000309 WO 2000-IB657 W 20000501 IN 2001-MN1305 A3 20011019 US 2002-979939 A3 20020606

OTHER SOURCE(S):

MARPAT 133:362656

GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

The antitumor agents, 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilones I (Rla, R1b are same or different = H, C1-C10 alkyl, C6-C12 aryl, C7-C20 aralkyl each optionally substituted; or together = (CH2)m m = 1-5 or -CH2OCH2-; R2a(R2b replace a with b) = H, substituted alkyl, aryl, aralkyl, (CH2)ra-C.tplbond.(or =)C-(CH2)pa-R26a, Q, Q1 where n = 0-5; ra, rb = the same or different and = 0-4; pa, pb = the same or different and = 0-3; R3a = H, substituted alkyl, aryl or aralkyl; R3b = OH, OPG14; R14 = H, OR14a, halogen and R14a = H, SO2-alkyl, SO2-aryl or SO2-aralkyl; R4 = H, substituted alkyl, aryl or aralkyl; halogen, OR25, CN; R26a, R26b = same or different = H, substituted alkyl, aryl or aralkyl, C1-C10 acyl or if pa or pb > 0, addnl. a group OR27; R25 = R27 = R22 = H, PG; R5 = H, substituted alkyl, aryl or aralkyl, (CH2)sT s = 1-4, T = OR22 or halogen; R6, R7 = H or together = bond or O; G = X=CR8 or bi- or tricyclic aryl radical and R8 = H, halogen, CN, or substituted alkyl, aryl or aralkyl; X = 0, two OR23 groups, C2-C10-alkylene- $\alpha$ , $\omega$ -dioxy straight chain or branched; H/OR9 or CR10R11 group and R23 = alkyl radical, R9 = H, PG, R10,R11 = same or different = H, substituted alkyl, aryl or aralkyl, or together with the methylene are a 5-7 carbocyclic ring; D-E = CH2CH2 or OCH2; A = OC(O), OCH2, CH2C(O), NR29C(O), NR29SO2 and R29 = H, alkyl; Z = O or H/OR12 and R12 = H, PG) were prepared Thus II was prepared in a multistep synthesis starting from (4S)-4-(2-methyl-1-oxoprop-2-yl)-2,2-dimethyl[1,3]dioxane and 5trimethylsilylpent-4-in-1-yl magnesium bromide. II had an IC50 value [nM] of 3.0 for the growth inhibition of human MCF-7 breast- and 75 for multidrug resistant NCI/ADR carcinoma cell lines with a selectivity of 2.5. The new epothilone derivs. interact with tubulin by stabilizing microtubuli that are formed. They are able to influence the cell-splitting in a phase-specific manner and are therefore useful in treating diseases or conditions associated with the need for cell growth, division and/or proliferation. Thus the growth is seen to be a se epothilone derivs. are suitable for treating malignant tumors, e.g., ovarian, stomach, colon, adeno-, breast, lung, head and neck carcinomas, malignant melanoma, acute lymphocytic and myelocytic leukemia; and for anti-angiogenesis therapy as well as for treatment of chronic inflammatory diseases (such as psoriasis, arthritis).

#### 303154-56-5P 303154-58-7P 303154-59-8P ΙT 303154-60-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilone derivs. and their use in pharmaceutical prepns.)

RN303154--56-5 ZCAPLUS

LLONG BEECH FLESS 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

CN

2 30

## SN 10/563058 Page 30 of 69 STIC STN SEARCH RESULTS

L25 ANSWER 10 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2000:790507 ZCAPLUS Full-text

DOCUMENT NUMBER:

133:362656

TITLE:

Preparation of 6-alkenyl-, 6-alkynyl- and

6-epoxyepothilone derivatives and their antitumor

activity

INVENTOR(S):

Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Hoffmann, Jens; Lichtner, Rosemarie

PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany

SOURCE:

PCT Int. Appl., 298 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PA	CENT I	NO.			KINI	)	DATE			APPL	ICAT	ION 1	<b>10.</b>	DATE				
WO	2000	0665	89							WO 2000-IB657				20000501				
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	ΑZ,	BA,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CR,	
		CU,	CZ,	DE,	DK,	DM,	DZ,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	GM,	HR,	HU,	
		-	-	-	-		KE,			-				-	-	-	-	
		LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	
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	RW:			-	•		SD,								•		•	
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							GW,								_			
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	2001		78 -		A						2001-							
	2001										2001-							
	7125						2006											
	2005										2005-							
	2006										2005-							
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#### SN 10/563058 Page 29 of 69 STIC STN SEARCH RESULTS

PATENT ASSIGNEE(S):

Bristol-Myers Squibb Company, USA

SOURCE:

PCT Int. Appl., 28 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

1

PATENT INFORMATION:

PATENT NO.					KIND DATE		APPLICATION NO.					DATE						
		2001						2001		,	WO 2	001-	JS96:	20		·	0010	323
	WO	2,001	0731	03		<b>A</b> 3		2002	0523									
		W:	ΑE,	ΑG,	AL,	AM,	ΑT,	ΑU,	AZ,	BA,	BB,	BG,	BR,	BY,	ΒZ,	CA,	CH,	CN,
			CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	GM,
•			HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KP,	KR,	ΚZ,	LC,	LK,	LR,	LS,
								MG,										
			RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	TM,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,
			VN,	YU,	ZA,	ZW,	ΑM,	ΑZ,	BY,	KG,	ΚZ,	MD,	RU,	ТJ,	TM			
,		RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	UG,	ZW,	AT,	BE,	CH,	CY,
			DE,	DK,	ES,	FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	TR,	BF,
			ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GW,	ML,	MR,	NE,	SN,	TD,	TG		
	US	2002	0421	09		A1		2002	0411		US 2	001-	8118	80		2	0010	319
	US	6593	115	_		B2		2003	0715									
	US	2004	0233	45		A1		2004	0205		US 2	003-	4470	82		2	0030	528
PRIO	RIT	Y APP	LN.	INFO	. :						US 2	000-	1919	75P		P 2	0000	324
											ÚS 2	001-	8118	80		A3 2	0010	319

OTHER SOURCE(S):

CASREACT 135:287591; MARPAT 135:287591

AB The present invention relates to a process for the preparation of intermediates useful in the synthesis of epothilone analogs by initially enzymically degrading certain epothilone compds. to form ring-open structures containing a carboxyl group which is esterified, the hydroxyl groups on the moiety protected and the resulting compound oxidized by, e.g. ozone, to form a first intermediate. The first intermediate can be reacted with a triphenylphosphine adduct to yield a compound containing an ester group at position 1 which is subsequently hydrolyzed to form a second intermediate.

IT 364336-79-8P 364336-83-4P

RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation of epothilone intermediates)

RN 364336-79-8 ZCAPLUS

CN Dodecanoic acid, 3,7-dihydroxy-4,4,6,8-tetramethyl-5,12-dioxo-, methyl ester, (3S,6R,7S,8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 364336-83-4 ZCAPLUS

CN Dodecanoic acid, 3,7-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-tetramethyl-5,12-dioxo-, methyl ester, (3S,6R,7S,8S)- (9CI) (CA INDEX NAME)

# SN 10/563058 Page 28 of 69 STIC STN SEARCH RESULTS

RN 303154-59-8 ZCAPLUS

CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry

RN 303154-60-1 ZCAPLUS

CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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L25 ANSWER 9 OF 25

ZCAPLUS COPYRIGHT 2007 ACS on STN 2001:731069 ZCAPLUS Full-text

ACCESSION NUMBER:

2001:731069 ZCAPLUS 135:287591

TITLE:

Preparation of epothilone intermediates

INVENTOR(S):

Vite, Gregory D.; Kim, Soong-Hoon; Hoeefle, Gerhard

#### SN 10/563058 Page 27 of 69 STIC STN SEARCH RESULTS

#### 303154-59-8P 303154-60-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 12,13-cyclopropylepothilone derivs. and their use in pharmaceutical compns.)

RN 303154-56-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-57-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-58-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 69 of 69 STIC STN SEARCH RESULTS

FILE BEILSTEIN
FILE LAST UPDATED ON September 26, 2007

FILE COVERS 1771 TO 2007.

FILE CONTAINS 10.119,480 SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

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- \* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.
- \* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE
- \* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE
- \* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.
- \* FOR PRICE INFORMATION SEE HELP COST

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- \* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.

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\* NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.

FILE BABS
FILE LAST UPDATED: 25 JUN 2007 <20070625/UP>
FILE COVERS 1980 TO DATE.

3. 2.3 F33

69

# SN 10/563058 Page 26 of 69 STIC STN SEARCH RESULTS

(CH2) pR26

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10041470 PRIORITY APPLN. INFO.:	A1	20020228	DE 2000-10041470 DE 2000-10041470	20000818 20000818
OTHER SOURCE(S):	CASREA	CT 136:21659	2; MARPAT 136:216592	

$$X^2 = (CH_2)_m - (CH_2)_p R^{26}$$

(CH2) m-

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The present invention describes new 6-alkenyl- and 6-alkynylepothilone AB derivs., e.g., I [Rla, Rlb = H, Cl-10-alkyl, aryl, C7-20-aralkyl; RlaRlb = (CH2)r, CH2OCH2; r = 1 - 5; R2a = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)m-C.tplbond.C-(CH2)pR26, (CH2)m-C:C-(CH2)pR26, X1, X2; n = 0 - 5; p = 0 - 3; m = 00 - 4; R2b = (CH2)m-C.tplbond.C-(CH2)pR26, (CH2)m-C:C-(CH2)pR26, X1, X2; R3a= H, C1-10-alkyl, aryl, C7-20-aralkyl; R3b = O-protecting group; R4 = H, C1-10-alkyl, aryl, C7-20-aralkyl, halogen, OH, O-protecting group, CN; R5 = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)s-T; S=1-4; T=OH, O-protecting-group, halogen; R6R7 = C(R33)2, NR32 AY = OC(:O), OCH2, CH2C(:O), NR29C(:O), -NR29SO2; DE = CH2CH2, CH2O, OCH2; G = X:CR8-, bicyclic or tricyclic aryl; X = O, (O-alkyl)2, etc.; Z = H, H,OH, H,O-protective group; R8 = H, halogen, CN, C1-20-alkyl, aryl, C7-20-aralkyl; R14 = H, OH, halogen, O-SO2-alkyl, O-SO2aryl, O-SO2-aralkyl; R26 = H, C1-10-alkyl, aryl, C7-20-aralkyl, C1-10-acyl, OH, O-protecting group; R29 = H, C1-20-alkyl; R32 = H, C1-4-alkyl, C1-4-acyl; R33 = H, halogen], which interact with tubulins by stabilizing the formed microtubulins (no data). I are able specifically to affect cell division and are suitable, for example for the treatment of malignant tumors ovarial -, stomach -, colon -, adeno -, chest -, lungs -, head and neck carcinoma, malignant melanoma, acute lymphocytic and myelocytic leukemia. In addition I are suitable for the anti-angiogenesis therapy as well as for the treatment of chronic ignitable illnesses (psoriasis, arthritis). For the avoidance of uncontrolled cell rampant growths on as well as the better compatibility of medical implants I can be up and/or brought into polymers materials. According to invention, I can be used alone or for the achievement of additive or synergistic effects in combination with further principles and substance classes applicable in the tumor therapy. Exptl. data from patents PCT/EP00/01333 and PCT/IB00/00657 are reproduced here. IT

303154-56-5P 303154-57-6P 303154-58-7P

#### SN 10/563058 Page 25 of 69 STIC STN SEARCH RESULTS

Ι

AΒ A facile and efficient route to epothilone analogs has been developed from the natural product epothilone D (I). Degradation of I via an oxidative cleavage sequence provides acid intermediate II rapidly in six steps. From II, a variety of epothilone analogs have been prepared utilizing ring-closing metathesis to reconstruct the trisubstituted-12,13-double bond. Using this approach, we report a number of epothilone analogs with varying C-15 aromatic side chains and C-14 allylic substitutions and their antitumor activities.

IT 681259-79-0P

> RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of epothilone D analogs via semisynthetic degradation and ring-closing metathesis and their antitumor activity)

RN681259-79-0 ZCAPLUS

Tridecanoic acid, 3,7-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-CN tetramethyl-5,12-dioxo-, methyl ester, (3S,6R,7S,8S)- (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 8 OF 25 ACCESSION NUMBER:

CAPLUS COPYRIGHT 2007 ACS on STN 2002:157050 ZCAPLUS Full-text

DOCUMENT NUMBER

136:216592

TITLE:

Procedures for the production of 12,13-

cyclopropylepothilone derivatives, as well as for

their use in pharmaceutical preparations

PATENT ASSIGNEE(S):

SOURCE:

Schering Ag, Germany

Ger. Offen., 64 pp.

CODEN: GWXXBX

14

DOCUMENT TYPE:

Patent German

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

## SN 10/563058 Page 24 of 69 STIC STN SEARCH RESULTS

RN 823203-24-3 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4S,5R,6S)-(CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 7 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2004:106102 ZCAPLUS Full-text

DOCUMENT NUMBER:

140:357084

TITLE:

Rapid access to epothilone analogs via semisynthetic

degradation and reconstruction of epothilone D

AUTHOR(S):

Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.;

Petryka, Joseph; Liu, Fenghua; Myles, David C.

CORPORATE SOURCE:

Department of Chemistry, Kosan Biosciences, Hayward,

CA, 94545, USA

SOURCE:

Tetrahedron Letters (2004), 45(9), 1945-1947

CODEN: TELEAY; ISSN: 0040-4039

PUBLISHER:

Elsevier Science B.V.

DOCUMENT TYPE:

Journal

LANGUAGE:

English

OTHER SOURCE(S):

CASREACT 140:357084

GΙ

# SN 10/563058 Page 23 of 69 STIC STN SEARCH RESULTS

RN 823203-04-9 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(2-propenyl)-, (4R,5S,6S,10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-05-0 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(2-propenyl)-, (4R,5S,6S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-23-2 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4R,5S,6S)-(CA INDEX NAME)

## SN 10/563058 Page 22 of 69 STIC STN SEARCH RESULTS

RN 220774-59-4 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-56-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-57-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 21 of 69 STIC STN SEARCH RESULTS

823203-04-9P 823203-05-0P 823203-23-2P 823203-24-3P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and tetrahydropyranylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof) RN 220774-19-6 ZCAPLUS 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-CN dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4R, 5S, 6S) - (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-20-9 ZCAPLUS CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dioxan-4-yl]-10-[[(1,1-dioxan-4-yl]-10-[(1,1-d

dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4S, 5R, 6S) - (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-58-3 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4R, 5S, 6S) - (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 20 of 69 STIC STN SEARCH RESULTS

#### IT 823203-07-2P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and perruthenate oxidation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 823203-07-2 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

#### IT 823203-19-6P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and silylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 823203-19-6 ZCAPLUS

CN 2,9-Tridecanedione, 7,11,13-trihydroxy-6,10,10-trimethyl-8-(2-propenyl)-, (6S,7S,8R,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 220774-19-6P 220774-20-9P 220774-58-3P 220774-59-4P 303154-56-5P 303154-57-6P

# SN 10/563058 Page 19 of 69 STIC STN SEARCH RESULTS

preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and detetrahydropyranylation of; method for producing C1-C15
 fragments of epothilones and derivs. thereof)

RN 823203-17-4 ZCAPLUS

CN 3-Nonanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-5-hydroxy-2,6-dimethyl-9-(2-methyl-1,3-dioxolan-2-yl)-4-(2-propenyl)-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-18-5 ZCAPLUS

1. -1 -11-12

CN 3-Nonanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-5-hydroxy-2,6-dimethyl-9-(2-methyl-1,3-dioxolan-2-yl)-4-(2-propenyl)-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

#### IT 220774-23-2P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and detrahydropyranylation/deketalization of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

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RN 220774-23-2 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-8-ethyl-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA'INDEX NAME)

# SN 10/563058 Page 18 of 69 STIC STN SEARCH RESULTS

RN 823203-06-1 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(2-propenyl)-5[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-25-4 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,4,6-trimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (CA INDEX NAME)

Absolute stereochemistry.

#### IT 823203-17-4P 823203-18-5P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic

#### SN 10/563058 Page 17 of 69 STIC STN SEARCH RESULTS

# IT 220774-21-0P 220774-60-7P 303154-58-7P 823203-06-1P 823203-25-4P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and desilylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 220774-21-0 ZCAPLUS

Absolute stereochemistry.

RN 220774-60-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(phenylmethyl)-5[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-58-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

#### SN 10/563058 Page 16 of 69 STIC STN SEARCH RESULTS

trimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (CA INDEX NAME)

Absolute stereochemistry.

#### IT 823203-08-3P 823203-20-9P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and Wittig reaction of, with (benzothiazolylpropyl)phosphonium iodide derivative; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 823203-08-3 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(2-propenyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-20-9 ZCAPLUS

CN 2,9-Tridecanedione, 7,11,13-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,10,10-trimethyl-8-(2-propenyl)-, (6S,7S,8R,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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#### SN 10/563058 Page 15 of 69 STIC STN SEARCH RESULTS

RN 220774-22-1 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-4-ethyl-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-61-8 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-59-8 ZCAPLUS

CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl).oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-27-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,4,6-

#### SN 10/563058 Page 14 of 69 STIC STN SEARCH RESULTS

RN 220775-76-8 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,8,10-trimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-60-1 ZCAPLUS

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2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-02-7 ZCAPLUS

CN 2,9-Tridecanedione, 8-ethyl-7,11,13-trihydroxy-6,10,10-trimethyl-, (6S,7S,8R,11S)- (CA INDEX NAME)

Absolute stereochemistry.

IT 220774-22-1P 220774-61-8P 303154-59-8P 823203-27-6P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and Swern oxidation of; method for producing C1-C15 fragments

of epothilones and derivs. thereof)

#### SN 10/563058 Page 13 of 69 STIC STN SEARCH RESULTS

alkyl, aryl, C7-20-aralkyl; R6, R7 = H; R6R7 = bond, O; G = X:CR8, bi- or tricyclic aryl; R8 = H, halogen, (un) substituted C1-20-alkyl, aryl, C7-20aralkyl; X = O, (OR23)2, C2-10-alkylene-  $\alpha$ ,  $\omega$ -dioxy, H(OR9), CR10R11; R23 = C1-20-alkyl; R9 = H, protecting group; R10, R11 = H, C1-10-alkyl, aryl, C7-20aralkyl; CR10R11 = 5 - to 7-membered carbocycle; R13 = CH2OR13a, CH2-halo, CHO, CO2R13b, CO-halo; R13a, R14a = H, SO2alkyl, SO2-aryl, SO2-aralkyl; R13aR14a = (CH2)o, CR15aR15b; o = 2 - 4; R13b, R14b = H, C1-10-alkyl, aryl,C7-20-aralkyl; R15a, R15b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15aR15b = (CH2)q; q = 3 - 6; R20 = O-PG, NHR29, N3; Z = O, H(OR12); R12 = H, PG] ofepothilones and derivs. The procedure comprises the bonding of a C1-C6 Fragment, R13CH2CHR14CR1aR1bC(:O)CHR2aR2b, to a C7-C12 fragment, R5C(:V)(CH2)3CR4aR4bC(:W)R3a [V, W = O, (OR23)2, C2-10-alkylene- $\alpha$ , $\omega$ -dioxy, H(OR9)], to form a C1-C12 fragment, R5C(:V)(CH2)3CR4aR4bCR3a(O-PG14)CR2aR2bC(:Z)CR1aR1bCHR14CH2R13 [PG = H, protecting group], which is then treated with a C13-C15 fragment, G-CR20'CH2CHR7'R21 [R7' = H; R20' = halogen, N3, NHR29, OH, O-PG, NR29-PG, C1-20-(perfluoro)alkylsulfonyloxy, (C1-4-alkyl, NO2, Cl, Br-substituted) benzyloxy, NR29SO2Me, NR29C(:O)Me, CH2C(:O)Me; R21 = OH, halo, O-PG, P+Ph3Hal- (Hal = F, Cl, Br, I), P(O)(OQ)2 (Q = C1-10-alkyl, Ph), P(:0) Ph2; R29 = H, C1-6-alkyl], to form the C1-C15 epothilone intermediate product I. Thus, I [Rla = Rlb = R5 = Me, R2a = CH2CH: CH2- $\beta$ , R2b  $R4b = H-\alpha_{S}R3 = H-\beta$ ,  $R4a = Me-\beta$ , R6R7 = bond, R13 = CO2H, R14 = OSiMe2CMe3as $\beta$ , R20 = OSiMe2CMe3- $\alpha$ , G = 2-methylbenzothiazol-5- yl, PG = SiMe2CMe3, Z = O] was prepared from (S)-4-(2-methyl-3-oxohept-6-en-2-yl)-2,2-dimethyl-1,3dioxane via lithiation and reaction with (2S,6RS)-2-methyl-6-[(tertbutyldimethylsilyl)oxy]heptanal, tetrahydropyranylation, desilylation with Bu4NF in THF, oxidation in CH2Cl2 containing N-methylmorpholine N-oxide and catalytic tetrapropylammonium perruthenate, Wittig reaction with [(3S)-3-(2methylbenzothiazol-5- yl)propyl]triphenylphosphonium iodide, deisopropylidenation/detetrahydropy ranylation with catalytic 4-MeC6H4SO3H in EtOH, silylation with CF3SO2SiMe2CMe3, regionelective desilylation with  $(\pm)$ camphor-10- sulfonic acid, Swern oxidation with DMSO/(COC1)2 in CH2C12 and carbonyl oxidation with NaOCl2 in aqueous THF/Me3COH. The produced C1-C15 epothilone intermediate products can be converted into the intrinsically active ingredients II [AK = OC(:0), OCH2, CH2C(:0), NR29C(:0), NR29SO2; R29 = H, C1-6-alkyl] according to known methods. The invention also relates to the corresponding C1-C12 fragments.

#### IT 220774-62-9P 220775-76-8P 303154-60-1P 823203-02-7P

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 220774-62-9 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(phenylmethyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

#### SN 10/563058 Page 12 of 69 STIC STN SEARCH RESULTS

Skuballa, Werner

PATENT ASSIGNEE(S):

Schering Aktiengesellschaft, Germany

SOURCE:

PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.							APPLICATION NO.					DATE							
· • ,	WO 2005003071				 A1				1	WO 2004-EP6685				2	0040	CH, GE, LK, NO, TJ, AM, DK, SE,			
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			CN,	CO,	CR,	CU,	CZ,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,	GE,	
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			LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NI,	NO,	
			ΝZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,	ТJ,	
			TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	zw		
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R6 R5 <sub>R</sub>7 R1? R4

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AΒ The invention relates to a method for preparing C1-C15 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; RlaRlb = (CH2)m; m = 2 - 5; R2a, R2b = H, C1-10-alkyl, C2-10-alkenyl, C2-10-alkynyl, aryl, C7-20-aralkyl; R2aR2b = (CH2)n; n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = H,C1-10-alkyl, aryl, C7-20-aralkyl; R4aR4b = (CH2)p; p = 2 - 5; R5 = H, C1-10-

#### SN 10/563058 Page 11 of 69 STIC STN SEARCH RESULTS

AB Synthesis of C1-C12 segment of epothilones A and B was achieved via diastereo-and regioselective opening of a trisubstituted epoxy ketone at the more substituted carbon. Epoxide I (R = SiMe2CMe3, R1 = benzyl) was cleaved selectively at the more substituted carbon using SmI2 in MeOH/THF at -90° to form the silyl protected  $\beta$ -hydroxyketone II which contains the C5-C7 epothilone aldol moiety.

IT 201683-59-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of C1-C12 segment of epothilones A and B via radical induced opening of trisubstituted epoxides)

RN 201683-59-2 ZCAPLUS

CN Dodecanoic acid, 7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-hydroxy-4,4,6,8-tetramethyl-5-oxo-12-(phenylmethoxy)-, 1,1-dimethylethyl ester, [3S-(3R\*,6S\*,7R\*,8R\*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 201683-49-0P

RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of C1-C12 segment of epothilones A and B via rad-

(synthesis of C1-C12 segment of epothilones A and B via radical induced opening of trisubstituted epoxides)

RN 201683-49-0 ZCAPLUS

CN Dodecanoic acid, 3,7-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-tetramethyl-5-oxo-12-(phenylmethoxy)-, 1,1-dimethylethyl ester, [3S-(3R\*,6S\*,7R\*,8R\*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL GITATIONS AVAILABLE IN THE RESERVANT

L25 ANSWER 6 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2
DOCUMENT NUMBER: 1

2005:29293 ZCAPLUS Full-text

142:113814

TITLE:

· · · · \*;

Method for producing C1-C15 fragments of epothilones

and derivatives thereof

INVENTOR(S):

Klar, Ulrich; Buchmann, Bernd; Schwede, Wolfgang;

#### SN 10/563058 Page 10 of 69 STIC STN SEARCH RESULTS

RN 346652-91-3 ZCAPLUS

CN Dodecanal, 6,10,12-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,9-tetramethyl-8-oxo-, (5S,6S,7R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L25 ANSWER 5 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5

ACCESSION NUMBER:

1998:14400 ZCAPLUS <u>Full-text</u>

DOCUMENT NUMBER:

128:114806

TITLE:

Radical-induced opening of trisubstituted epoxides: application in the synthesis of C1-C12 segment of

epothilones

AUTHOR(S):

Chakraborty, T. K.; Dutta, S.

CORPORATE SOURCE:

Indian Inst. Chem. Technol., Hyderabad, 500 007, India

SOURCE:

Tetrahedron Letters (1998), 39(1/2), 101-104

CODEN: TELEAY; ISSN: 0040-4039

PUBLISHER:

Elsevier Science Ltd.

DOCUMENT TYPE:

Journal

LANGUAGE:

English

OTHER SOURCE(S):

CASREACT 128:114806

GΙ

#### SN 10/563058 Page 9 of 69 STIC STN SEARCH RESULTS

AB Naturally occurring epothilones have been synthesized starting from enantiomerically pure aldol compds. I and II, which were obtained by antibody catalysis. Aldolase antibody 38C2 catalyzed the resolution of (±)-I by enantioselective retro-aldol reaction to afford I in 90% ee at 50% conversion. Compds. II (R = Me, CH2OH) were obtained in more than 99% ee at 50% conversion by resolution of their racemic mixts. using newly developed aldolase antibodies 84G3, 85H6 or 93F3. Compds. I and II were resolved in multigram quantities and then converted to the epothilones by metathesis processes, which were catalyzed by Grubbs' catalysts.

IT 346651-96-5P

RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilones A-F)

RN 346651-96-5 ZCAPLUS

CN 2,9-Tridecanedione, 7,11,13-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,8,10,10-tetramethyl-, (6S,7S,8R,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 346652-88-8P 346652-91-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilones A-F)

RN 346652-88-8 ZCAPLUS

CN 4,12-Dioxa-3,13-disilapentadecan-7-one, 9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[(1S)-5-hydroxy-1-methylpentyl]-2,2,3,3,6,8,8,13,13,14,14-undecamethyl=3,(5S,6R,9S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

#### SN 10/563058 Page 8 of 69 STIC STN SEARCH RESULTS

CORPORATE SOURCE:

Abteilung Naturstoffchemie, Gesellschaft fuer Biotechnologische Forschung mbH, Braunschweig,

D-38124, Germany

SOURCE:

Journal of the Chemical Society, Perkin Transactions 1

(2002), (22), 2490-2503

CODEN: JCSPCE; ISSN: 1472-7781 Royal Society of Chemistry

PUBLISHER:
DOCUMENT TYPE:

Journal English

LANGUAGE:

Eng.

OTHER SOURCE(S):

CASREACT 138:187542

AB: Novel and unique chiral building blocks of high structural diversity were obtained by selective chemical fragmentation of natural products from myxobacteria. Subsequent modification reactions provided primary alc. and carboxylic acid derivs., which are suitable for the construction of combinatorial chemical libraries. The single SPOT synthesis of a hybrid structure on a polypropylene membrane was employed to demonstrate the chemical recombination of such rare building blocks on a micro-scale.

IT 498580-02-2P

RL: SPN (Synthetic preparation); PREP (Preparation) (fragmentation of natural products from myxobacteria as building blocks for combinatorial synthesis)

RN 498580-02-2 ZCAPLUS

CN Dodecanoic acid, 3,7,12-trihydroxy-4,4,6,8-tetramethyl-5-oxo-, methyl ester, (3S,6R,7S,8S)- (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 4 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4

ACCESSION NUMBER:

2001:316603 ZCAPLUS Full-text

DOCUMENT NUMBER:

135:76707

50

TITLE:

Catalytic antibody route to the naturally occurring epothilones: total synthesis of epothilones A - F

AUTHOR(S):

Sinha, Subhash C.; Sun, Jian; Miller, Gregory P.;

Wartmann, Markus; Lerner, Richard A.

CORPORATE SOURCE:

Department of Molecular Biology and the Skaggs

Institute for Chemical Biology, The Scripps Research

Institute, La Jolla, CA, 92037, USA

SOURCE:

Chemistry--A European Journal (2001), 7(8), 1691-1702

CODEN: CEUJED; ISSN: 0947-6539

PUBLISHER:

Wiley-VCH Verlag GmbH

DOCUMENT TYPE:

Journal

LANGUAGE:

English

OTHER SOURCE(S):

CASREACT 135:76707

GT

#### SN 10/563058 Page 7 of 69 STIC STN SEARCH RESULTS

CODEN: ACIEF5; ISSN: 1433-7851

Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE: Journal LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:197285

GΙ

PUBLISHER:

AB A total synthesis of epothilone C (I) with concomitant formal synthesis of epothilone A is described, using immobilized reagents and scavengers to effect multistep synthetic transformations and purifications.

IT 346652-91-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilones using solid-supported reagents and scavengers)

RN 346652-91-3 ZCAPLUS

CN Dodecanal, 6,10,12-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,9-tetramethyl-8-oxo-, (5S,6S,7R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3

ACCESSION NUMBER:

2002:863402 ZCAPLUS Full-text

TITLE:

138:187542 Natural product-derived building blocks for

combinatorial synthesis. Part 1. Fragmentation of

natural products from myxobacteria

AUTHOR(S):

Niggemann, Jutta; Michaelis, Katrin; Frank, Ronald;

Zander, Norbert; Hoefle, Gerhard

19 34 3

#### SN 10/563058 Page 6 of 69 STIC STN SEARCH RESULTS

AB The total synthesis of the cytotoxic antitumor natural product epothilone C has provided a stage for the exploitation and further development of immobilized reagent methods. A stereoselective convergent synthetic strategy was applied, incorporating polymer-supported reagents, catalysts, scavengers and catch-and-release techniques to avoid frequent aqueous work-up and chromatog. purification The enantioselective preparation of 3 key fragments heptanone I, (S)-2-methyl-6-heptenal, and thiazole II along with their elaboration via diastereoselective coupling into epothilone C is presented.

IT 346652-91-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilone C via asym. synthesis and stereoselective coupling of heptanone, methylheptenal, and thiazole fragments using immobilized reagents and scavengers)

RN 346652-91-3 ZCAPLUS

CN Dodecanal, 6,10,12-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,9-tetramethyl-8-oxo-, (5S,6S,7R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L25 ANSWER 2 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2

ACCESSION NUMBER:

2003:494861 ZCAPLUS Full-text

DOCUMENT NUMBER:

139:197285

TITLE:

A total synthesis of epothilones using solid-supported

reagents and scavengers

AUTHOR(S):

Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip

S.; Ley, Steven V.

CORPORATE SOURCE:

University Chemical Laboratories, University of

Cambridge, Cambridge, CB2 1EW, UK

SOURCE:

Angewandte Chemie, International Edition (2003),

42(22), 2521-2525

#### SN 10/563058 Page 5 of 69 STIC STN SEARCH RESULTS

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FILE LAST UPDATED:

25 JUN 2007

<20070625/UP>

FILE COVERS 1980 TO DATE.

=> d stat que L14

L14

7 SEA FILE=BABS ABB=ON PLU=ON (6300090/BABSAN OR 6630563/BABSAN OR 6085475/BABSAN OR 6376421/BABSAN OR 6410256/BABSAN OR 6473119/BABSAN OR 6597156/BABSAN)

and the second s => dup rem L6 L19 L14

DUPLICATE IS NOT AVAILABLE IN 'BEILSTEIN'.

ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE FILE 'ZCAPLUS' ENTERED AT 15:47:21 ON 11 OCT 2007

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PROCESSING COMPLETED FOR L6

PROCESSING COMPLETED FOR L19

PROCESSING COMPLETED FOR L14

25 DUP REM L6 L19 L14 (7 DUPLICATES REMOVED)

ANSWERS '1-18' FROM FILE ZCAPLUS ANSWERS '19-25' FROM FILE BEILSTEIN

=> d ibib abs hitstr L25 1-18; d ide allref L25 19-25

L25 ANSWER 1 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1

ACCESSION NUMBER:

2004:454851 ZCAPLUS Full-text

DOCUMENT NUMBER:

141:140221

TITLE:

Multi-step application of immobilized reagents and

scavengers: A total synthesis of epothilone C

AUTHOR(S):

Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip S.; Brown, Dearg S.; Baxendale, Ian R.; Ley, Steven V.

6 2 5 CORPORATE SOURCE:

Department of Chemistry, University of Cambridge,

Cambridge, CB2 1EW, UK

SOURCE:

Chemistry--A European Journal (2004), 10(10),

2529-2547

CODEN: CEUJED; ISSN: 0947-6539

PUBLISHER:

Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE:

Journal English

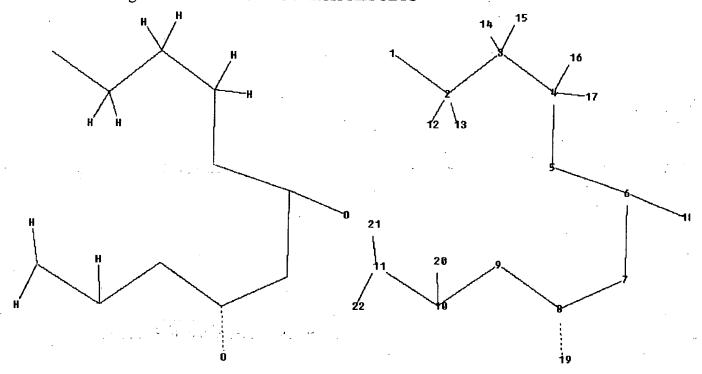
the growth of the

LANGUAGE: OTHER SOURCE(S):

CASREACT 141:140221

5

#### SN 10/563058 Page 4 of 69 STIC STN SEARCH RESULTS



```
chain nodes :
 12 13 14 15 16 17 18 19 20 21 22
 ring/chain nodes :
 1 2 3 4 5 6 7 8
                         9 10 11
 chain bonds :
 2-12 2-13 3-14 3-15 4-16 4-17 6-18 8-19 10-20 11-21 11-22
ring/chain bonds :
 1-2 2-3 3-4 4-5 5-6 6-7
                               7-8 8-9 9-10 10-11
 exact/norm bonds :
 1-2 2-3 3-4 4-5 5-6 6-7
                               6-18
                                     7-8 8-9 8-19 9-10 10-11
 exact bonds :
2 - 12 \quad 2 - 13 \quad 3 - 14 \quad 3 - 15 \quad 4 - 16 \quad 4 - 17 \quad 10 - 20 \quad 11 - 21 \quad 11 - 22
```

#### Match level:

1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS

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L3 SCR 1008

L11 38 SEA FILE=BEILSTEIN SSS FUL L1 AND L3

L12 26 SEA FILE=BEILSTEIN ABB=ON PLU=ON L11/COM

L13 5 SEA FILE=BEILSTEIN ABB=ON PLU=ON L12 AND BABSAN/FA

L15 21 SEA FILE=BEILSTEIN ABB=ON PLU=ON L12 NOT L13

L16 14 SEA FILE=BEILSTEIN ABB=ON PLU=ON L15 AND RN/FA

L19 7 SEA FILE=BEILSTEIN ABB=ON PLU=ON L15 NOT L16
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#### => file babs

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#### SN 10/563058 Page 3 of 69 STIC STN SEARCH RESULTS

FILE COVERS 1771 TO 2007.

\*\*\* FILE CONTAINS 10.119,480 SUBSTANCES \*\*\*

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<

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- \* NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.

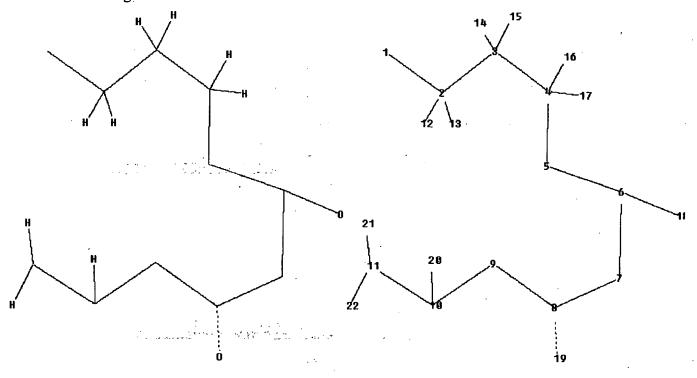
=> d stat que L19 L1STR

1 / 2000

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

Structure attributes must be viewed using STN Express query preparation: Uploading L1.str

#### SN 10/563058 Page 2 of 69 STIC STN SEARCH RESULTS



chain nodes :
12 13 14 15 16 17 18 19 20 21 22
ring/chain nodes :
1 2 3 4 5 6 7 8 9 10 11
chain bonds :
2-12 2-13 3-14 3-15 4-16 4-17 6-18 8-19 10-20 11-21 11-22
ring/chain bonds :
1-2 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11
exact/norm bonds :
1-2 2-3 3-4 4-5 5-6 6-7 6-18 7-8 8-9 8-19 9-10 10-11
exact bonds :
2-12 2-13 3-14 3-15 4-16 4-17 10-20 11-21 11-22

#### Match level:

1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS

L3 SCR 1008 L5 68 SEA FILE=REGISTRY SSS FUL L1 AND L3 L6 18 SEA FILE=ZCAPLUS ABB=ON PLU=ON L5

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STRUCTURE FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1 DICTIONARY FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

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#### http://www.cas.org/support/stngen/stndoc/properties.html

=> file zcaplus

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FILE COVERS 1907 - 11 Oct 2007 VOL 147 ISS 16 FILE LAST UPDATED: 10 Oct 2007 (20071010/ED)

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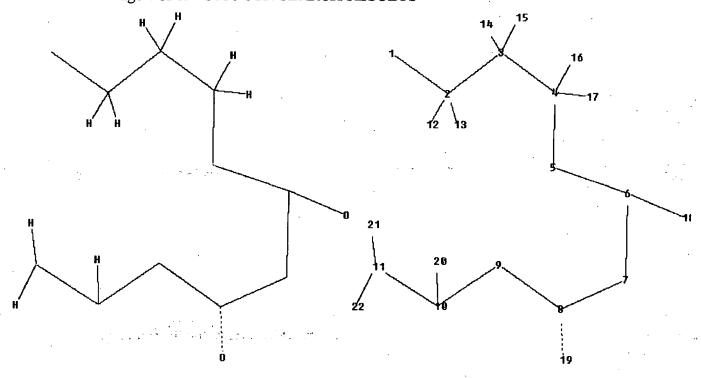
This file contains CAS Registry Numbers for easy and accurate substance identification.
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=> d stat que L6 L1 STR

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Structure attributes must be viewed using STN Express query preparation: Uploading L1.str

#### SN 10/563058 Page 4 of 69 STIC STN SEARCH RESULTS



```
chain nodes :
12 13 14 15 16 17 18 19 20 21 22
ring/chain nodes :
1 2 3 4 5 6 7 8
                       9 10 11
chain bonds :
2-12 2-13 3-14 3-15 4-16 4-17 6-18 8-19 10-20 11-21 11-22
ring/chain bonds :
1-2 2-3 3-4 4-5 5-6 6-7 7-8
                                    8-9 9-10 10-11
exact/norm bonds :
1-2 2-3 3-4 4-5 5-6 6-7
                               6-18
                                     7-8 8-9 8-19 9-10 10-11
exact bonds :
2 - 12 \quad 2 - 13 \quad 3 - 14 \quad 3 - 15 \quad 4 - 16 \quad 4 - 17 \quad 10 - 20 \quad 11 - 21 \quad 11 - 22
```

#### Match level:

1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS

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L3
               SCR 1008
L11
            38 SEA FILE=BEILSTEIN SSS FUL L1 AND L3
L12
            26 SEA FILE=BEILSTEIN ABB=ON PLU=ON L11/COM
L13
            5 SEA FILE=BEILSTEIN ABB=ON PLU=ON L12 AND BABSAN/FA
L15
          21 SEA FILE=BEILSTEIN ABB=ON PLU=ON L12 NOT L13
L16
            14 SEA FILE=BEILSTEIN ABB=ON
                                         PLU=ON L15 AND RN/FA
L19
             7 SEA FILE=BEILSTEIN ABB=ON
                                         PLU=ON L15 NOT L16
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#### => file babs

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\*\*\* FILE CONTAINS 10.119,480 SUBSTANCES \*\*\*

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN Compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE : <<<

- \* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.
- \* NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.

=> d stat que L19 L1 STR

1 100

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Structure attributes must be viewed using STN Express query preparation: Uploading L1.str

Interm al Application No

PCT/~:12004/006685 CLASSIFICATION OF SUBJECT MATTER IPC 7 C07C49/17 C07D417/06 C07D493/04 According to International Patent Classification (IPC) or to both national classification and IPC Minimum documentation searched (classification system followed by classification symbols) C07C C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, PAJ, BEILSTEIN Data, CHEM ABS Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X WO 99/07692 A (KLAR ULRICH; SCHERING AG 1-5 (DE); BUCHMANN BERND (DE); SKUBALLA WERNER () 18 February 1999 (1999-02-18) cited in the application page 49, lime 1 - page 50, lime 15; claim US 2003/0144523 Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents: tater document published after the international filing date or priority date and not in conflict with the application but died to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance Invention earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken atone filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person sidiled "O" document referring to an oral disclosure, use, exhibition or document published prior to the international filing date but later than the priority date claimed \*&\* document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 13 October 2004 20/10/2004 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentinan 2 NL - 2280 HV Riswilk Tel (+31-70) 340-2040, Tx. 31 651 epo nl Fac (+31-70) 340-3016 Seelmann, I

#### **Abstract**

This invention describes a process for the production of C<sub>1</sub>-C<sub>15</sub>-fragments of epothilones and derivatives thereof, in which a C1–C6-fragment is linked with a C7–C12-fragment to a C1–C12-fragment, and the latter then is reacted with a C13–C15-fragment to form the C1–C15 initial epothilone product that is to be produced.

The thus obtained C1-C15 initial epothilone products can be reacted according to known methods to form the actual active ingredients.

In addition, the invention relates to the corresponding C1-C12-fragments.

PATENT COOPERATION TREAT

PCT

10/563058 1SK

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference See Form PCT/IPEA/416 FOR FURTHER ACTION 53110AWO Priority date (day/month/year) International filing date (day/month/year) International application No. 03.07.2003 PCT/EP2004/006685 19.06.2004 International Patent Classification (IPC) or national classification and IPC C07C49/17, C07D417/06, C07D493/04 Applicant SCHERING AKTIENGESELLSCHAFT This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. This REPORT consists of a total of 5 sheets, including this cover sheet. This report is also accompanied by ANNEXES, comprising: (sent to the applicant and to the International Bureau) a total of sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions). This report contains indications relating to the following items: Box No. I Basis of the report Box No. Il Priority Non-establishment of opinion with regard to novelty, inventive step and industrial applicability Box No. III Box No. IV Lack of unity of invention Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; Box No. V citations and explanations supporting such statement Box No. VI Certain documents cited Box No. VII Certain defects in the international application Box No. VIII Certain observations on the international application Date of completion of this report Date of submission of the demand Authorized officer Name and mailing address of the IPEA/EP

Telephone No.

Facsimile No.

Translation

International application No.
PCT/EP2004/006685

Boy '	No. I	Basis of the report								
			of analysis - 2. ch - 1	as Glad unless -t '						
1.	indicate	regard to the language, this report is based on the internations ted under this item.								
	This report is based on translations from the original language into the following language which is the language of a translation furnished for the purposes of:									
	<u> </u>	international search (Rule 12.3 and 23.1(b))								
	Ē	publication of the international application (Rule 12.4)								
		international preliminary examination (Rule 55.2 and/o								
2.	With re receiving this rep	regard to the elements of the international application, this r ing Office in response to an invitation under Article 14 are sport):	report is based on (replacement sheets whi referred to in this report as "originally f	ch have been furnished to the iled" and are not annexed to						
		the international application as originally filed/furnished								
	$\square$	the description:								
[		pages 1-36		as originally filed/furnished						
ĺ	•	pages*								
	-	pages*								
	<b>N</b>									
	E-3 (	the claims:		as originally filed/furnished						
		nos. <u>1-5</u>								
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	_ '	nos.*	received by this Authority on							
	□ ,	the drawings:								
	s	sheets		as originally filed/furnished						
	S	sheets*	received by this Authority on							
	s	sheets*	received by this Authority on							
		a sequence listing and/or any related table(s) - see Supplement	ental Box Relating to Sequence Listing.							
3.		The amendments have resulted in the cancellation of:								
	_ [	the description, pages								
	۲	the claims, nos.								
	٢	the drawings, sheets/figs								
	L									
	ι Γ									
.	ا ا	any table(s) related to sequence listing (specify):  This report has been established as if (some of) the amend	dments annexed to this report and listed be							
4.	ر لـا	This report has been established as if (some of) the amend they have been considered to go beyond the disclosure as fil	led, as indicated in the Supplemental Box (	Rule 70.2(c)).						
	ĺ	the description, pages								
	{	the claims, nos.								
	[	the drawings, sheets/figs								
	[	the sequence listing (specify):								
	[	<u> </u>								
1.	If item	m 4 applies, some or all of those sheets may be marked "sup	erseded."							

International application No.
PCT/EP2004/006685

	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement						
Statement							
Novelty (N)	Claims		YES				
	Claims	1-5	NO				
Inventive step (IS)	Claims		YES				
	Claims	1-5	NO				
Industrial applicability (IA)	Claims	1-5	YES				
	Claims		МО				
	Citations and explosions  Novelty (N)  Inventive step (IS)	Claims  Novelty (N)  Claims  Claims  Inventive step (IS)  Claims  Claims  Claims  Claims  Claims	Statement				

#### 2. Citations and explanations (Rule 70.7)

The present application appears not to satisfy the requirements of PCT Article 33(2) because the subject matter of the claims is not novel. Claim 9 and pages 49-50 of the description of document D1 (WO 99/07692 A) concern, inter alia, a method for producing epothilone derivatives from the fragments A+B = A-B and A-B + C = A-BB-C, wherein all three fragments structurally overlap the A, B and C claimed in the present application. The formula AB in claim 9 of document D1 therefore appears to be prejudicial to the novelty of the present claim 5. The method of claim 9 of document D1 likewise appears to be prejudicial to the novelty of present claims 1-4. In particular, in the C fragment U=C-R appears to overlap with G in document D1, and in fragment AB CH-CH versus D-E in AB of document D1 does not result in a new selection, since D-E form a unit, that is to say, they cannot be selected independently of each other. Consequently, this is considered no more than a selection from a list.

Document D1 is the closest prior art. It discloses the production of epothilone derivatives from the fragments A+B=A-B and A-B+C=A-B-C. The problem to be solved

International application No.
PCT/EP2004/006685

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

by the present invention is understood to be that of providing an alternative method for producing epothilones. In the light of the experimental part it can be assumed that this problem is solved by the application. However, insofar as the subject matter of the present application can be considered novel, the fragments A, B and C are similar to those of document D1 to such an extent that the solution is obvious to a person skilled in the art. The problem to be solved by the present application must therefore be considered that of an alternative method having unexpected or surprising properties with respect to the closest prior art (D1). Without comparative test results or other arguments demonstrating the patentability of the invention it is not possible to assess whether the invention satisfies the requirements of PCT Article 33(3). The present application does not appear to meet the requirements of PCT Article 33(2) because the subject matter of the claims is not novel. Claim 9 and pages 49-50 of the description of document D1 (WO 99/07692 A) concern, inter alia, a method for producing epothilone derivatives from the fragments A+B = A-B and A-B+C = A-B-C, wherein all three fragments structurally overlap with the fragments A, B and C claimed in the present application. The formula AB in claim 9 of document D1 therefore appears to be prejudicial to the novelty of the present claim 5. The method of claim 9 of document D1 likewise appears to be prejudicial to the novelty of the present claims 1-4. In particular, in the C fragment, U=C-R appears to overlap with G in document D1, and in fragment AB, CH-CH as opposed to D-E in AB of document D1 does not lead to a novel selection, since D-E form a unit, that is to say,

International application No.
PCT/EP2004/006685

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

they cannot be selected independently of each other.

Consequently, this is considered no more than a selection from a list.

Document D1 is the closest prior art. It discloses the Production of epothilone derivatives from the fragments A+B = A-B and A-B + C = A-B-C. The problem to be solved by the present invention is understood to be that of providing an alternative method, for the production of epothilones. In the light of the experimental part, it can be assumed that this problem is solved in the application. However, insofar as the subject matter of the present application can be considered novel, the fragments A, B and C are similar to those of document D1 to such an extent that the solution is obvious to a person skilled in the art. The problem to be solved by the present application must therefore considered that of making available an alternative method having unexpected or surprising properties with respect to the closest prior art document (D1). Without comparative test results or other arguments demonstrating the patentability of the invention it is not possible to assess whether the invention satisfies the requirements of PCT Article 33(3).

#### Lao, MariaLouisa

From:

DiNatale, John

Sent:

Thursday, October 11, 2007 4:01 PM

To:

Lao, MariaLouisa

Subject:

10/563058

Examiner Lao,

Your search results for serial number 10/563058 are complete and have been submitted to SCORE for posting. Routinely these results will be posted as early as <u>tomorrow</u>. Please see the instructions at the bottom of this email for retrieving search results <u>from eDan 2.2.1</u>.

#### \*\*Search-specific notes:

The search results are located in 2 RTF files.

The organization of the search results within the RTF file called 20071011-10563058-str<u>1</u>.rtf is sequential, divided by page breaks:

- 1) author search
- 2) Claim 1 reaction search,
- 3) Claim 4 reaction search, and
- 4) search history.

The organization of the search results within the RTF file called 20071011-10563058-str2.rtf is sequential, divided by page breaks:

1) Claim 5 structure search

and

2) search history.

It may be helpful to save this memo as an index to the search results.

Please contact me if you have any questions.

Thank you, John DiNatale X2-2557

To access your search results via eDAN:

- 1) Enter Application number
- 2) Click on Supplemental Content Tab
- 3) <u>STN results</u> (structure and text searches) are under **Other Content** (click on version listed). <u>ABSS Sequence</u> results are under the **Search Results** (click on version listed).

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#### -3/BI OR 220774-19-6/BI OR 220774-20-9/BI OR 220774-21-0/BI OR 220774-22-1/BI OR 220774-23-2/BI OR 220774-57-2/BI OR 220774-58-2/BI OR 220774-58-2/BI OR 220774-58-2/BI OR 220774-58-2/BI OR 220774-58-2/BI OR 220774-58-2/BI OR 220774-6-6/BI OR 220774-6-6-1/BI OR 220774-6-6-9/BI OR 220774-6-9/BI OR 220774-6-6-9/BI OR 220774-6-9/BI OR 220774-6-9/BI OR 220774-6-6-9/BI OR 220774-6-6-9/BI OR 220774-70-1/BI OR 220775-76-8/BI OR 220777-70-6-9/BI OR 22077-70-6-9/BI OR 22077-70-6-9/BI OR 22077-70-6-9/BI OR 22077-70-6-9/BI OR 22077-70-6-9/BI OR 22077-70-6-9/BI OR 22073-6-9/BI OR 22073-6-9/BI OR 22073-6-9/BI OR 22073-6-9/BI OR 22073-6-9/BI OR 22073-6-9/BI OR 22073-10-9/BI OR 22073-11-8/BI OR 22073-12-9/BI OR 22073-11-8/BI OR 22073-12-9/BI OR 22073-13-9/BI OR 22073-13-9/BI OR 22073-13-9/BI OR 22073-13-9/BI OR 22073-13-9/BI OR 22073-22-9/BI OR 22073-27-9/BI OR 22073-3-27-9/BI OR 22073-27-9/BI OR 22073-3-27-9/BI OR 22073-3-27-9/BI OR 22073-27-9/BI OR 22073-3-27-9/BI OR 22073-27-9/BI OR 22073-27-9/BI OR 22073-27-FILE 'CASREACT' ENTERED AT 12:00:01 ON 11 OCT 2007 11 SEA ABB=ON PLJ=ON ("126:251010"/AN OR "127:108793"/AN OR "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR "131:286299"/AN OR "131:31819"/AN OR "131:366299"/AN OR "131:31819"/AN OR "1997:206419"/AN OR "1997:430390"/AN OR "1997:2665094"/AN OR "1999:372644794"/AN OR "1999:37364794"/AN OR "1999:373647/AN OR "1999:444724"/AN OR "1999:606636"/AN OR "1999:78/AN) FILE 'REGISTRY' ENTERED AT 11:54:40 ON 11 OCT 2007 E EPOTHILONE C/CN 'CASREACT' ENTERED AT 11:56:56 ON 11 OCT 2007 SN 10/563058 Page 169 of 172 STIC STN SEARCH RESULTS FILE 'CAPLUS' ENTERED AT 11:50:53 ON 11 OCT 2007 1 SEA ABB=ON PLU=ON L67 AND L65 D SCA 'CAPLUS' ENTERED AT 11:58:45 ON 11 OCT 2007 11 SEA ABB=ON PLU=ON L45 AND PY<2000 1 SEA ABB=ON PLU=ON EPOTHILONE C/CN EPOTHILONE D/CN L42 (L) L71 L42 (L) L72 (L73 OR L74) L75 NOT L60 (L) 1/NS (L) 2/NS L78 AND L43 L79 OR L52 L80 AND L73 L80 AND L74 L52 OR L79 OI SEA ABB=ON PLU=ON 166 AND L39 D SCA NOT L63 L43 180 180 152 161 1 SEA ABB=ON PLU=ON PLU-ON PLU=ON PLW-ON PLU-ON D RN L67 1-2 7 SEA ABB=ON 7 SEA ABB=ON 14 SEA ABB=ON SEA ABB-ON SEA ABB-ON 27 SEA ABB=ON 15 SEA ABB=ON D FHIT 7 SEA ABB=ON SEA ABB=ON 21 SEA ABB=ON 14 SEA ABB=ON 13 SEA ABB=ON SEA ABB=ON SEA ABB-ON -6/BI) SCA SCA Δ FILE FILE 170 L71 L72 L73 L74 L75 177 1.79 1.80 1.81 1.83 1.83 185 186

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1.67

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13 SEA ABBENN PULLENN L43 (L) 3/NS 13 SEA ABBENN PULLENN L43 (L) 3/NS 13 SEA ABBENN PULLENN L43 (L) 4/NS 12 SEA ABBENN PULLENN L43 (L) 5/NS 12 SEA ABBENN PULLENN L43 (L) 5/NS 12 SEA ABBENN PULLENN L43 (L) 5/NS 16 SEA ABBENN PULLENN RATAR U7/AU 16 SEA ABBENN PULLENN SCHWENLIA W7/AU 16 SEA ABBENN PULLENN SCHWENLIA W7/AU 18 SEA ABBENN PULLENN SCHWENLIA W7/AU 18 SEA ABBENN PULLENN L92 AND (L92 OR L93) 12 SEA ABBENN PULLENN L93 AND (L93 OR L94) 13 SEA ABBENN PULLENN L93 AND (L94 OR L94) 14 SEA ABBENN PULLENN L93 AND (L95 OR L94) 15 SEA ABBENN PULLENN L93 AND (196 OR L97) 16 SEA ABBENN PULLENN L93 AND (196 OR L97) 17 SEA ABBENN PULLENN L93 AND (196 OR L97) 18 SEA ABBENN PULLENN L93 AND (196 OR L97)	1 SEA ABB=ON PLU=ON 120 AND 1 SEA ABB=ON PLU=ON 1100 AND 1 SEA ABB=ON PLU=ON 1100 AND 1 SEA ABB=ON PLU=ON 111:27 ON 1 CAPLUS' ENTERED AT 12:11:29 ON 11 D STAT QUE 1100 D STAT ABS 1100 1-24	1818 ABS	'REGISTRY' ENTERED AT 12:16:30 ON 11 OCT 2007 'CASREACT' ENTERED AT 12:16:34 ON 11 OCT 2007 D STAT QUE L33 D IBIB ABS FHIT L33 1-23	'CASREACT' ENTERED AT 12:18:14 ON 11 OCT 2007  D STAT QUE L90  D IBIB ABS FHIT L90 1-28  3 SEA ABB=ON PLU=ON L77 NOT L90  3 SEA ABB=ON PLU=ON L78 NOT L90	'CAPLUS' ENTERED AT 12:40:57 ON 11 OCT 2007 21 SEA ABB=ON PIJJ=ON L45 AND PY<2001 SEL AN	'CASREACT' ENTERED AT 12:41:26 ON 11 OCT 2007 21 SEA ABB=ON PLU=ON ("126:251010"/AN OR "127:108793"/AN OR "1127:293040"/AN OR "128:101096"/AN OR "123:198151"/AN OR "131:19855"/AN OR "131:386299"/AN OR "131:31819"/AN OR "131:38227"/AN OR "131:386299"/AN OR "131:31819"/AN OR "131:38227"/AN OR "131:351125"/AN OR "133:26251"/AN OR "132:2521011"/AN OR "133:26252"/AN OR "134:76257"/AN OR "134:76257"/AN OR "134:76257"/AN OR "134:762679"/AN OR "134:76309"/AN OR "1997:266419"/AN OR "1999:37009"/AN OR "1999:3720444724"/AN OR "1999:37204740"/AN OR "1999:37204740"/AN OR "1999:3720444724"/AN OR "1999:37204404724"/AN OR "1999:3720"/AN OR "1999:37204404724"/AN OR "1999:3720"/AN OR "1999:3720"/AN OR "1999:3720440"/AN OR "1999:3720"/AN OR "1999:3720"/AN OR "1999:3720"/AN OR "1999:3720"/AN OR "1999:3720"/AN OR "1999:3720"/AN OR "1999:3720440"/AN OR "1999:3720"/AN OR "1990:3720"/AN OR "1990 "AN OR "199	
FILE 'C	FILE		FILE	FILE	FILE	FILE	
11.12 1.88 1.89 1.92 1.93 1.94 1.95 1.96 1.96	1100 1101	L102		L103	L105	1106	

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"1999; 606636"/AN OR "1999:819379"/AN OR "2000:514132"/AN OR "2000:52837"/AN OR "2000:55974"/AN OR "2000:559403"/AN OR "2000:579403"/AN OR "2000:701228"/AN OR "2000:733774"/AN OR "2000:64216"/AN OR "2000:65345"/AN OR "2000:84216"/AN OR "2000:853645"/AN OR "2001:843887"/AN)
SEA ABB=ON PLIJ-ON L106 NOT L90
SEA ABB=ON PLIJ-ON L106 AND L43
SEA ABB=ON PLIJ-ON L106 NOT L90 D STAT QUE L109 D IBIB ABS FHIT L109 1-7 7 SEA ABB=ON 21 SEA ABB=ON 7 SEA ABB=ON

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